Pergamon

Tetrahedron Vol. 51, No. 43, pp. 11693-11702, 1995
Copyright © 1995 Elsevier Science Ltd
Printed in Great Britain. All rights reserved
0040-4020/95 $9.50+0.00

0040-4020(95)00701-6

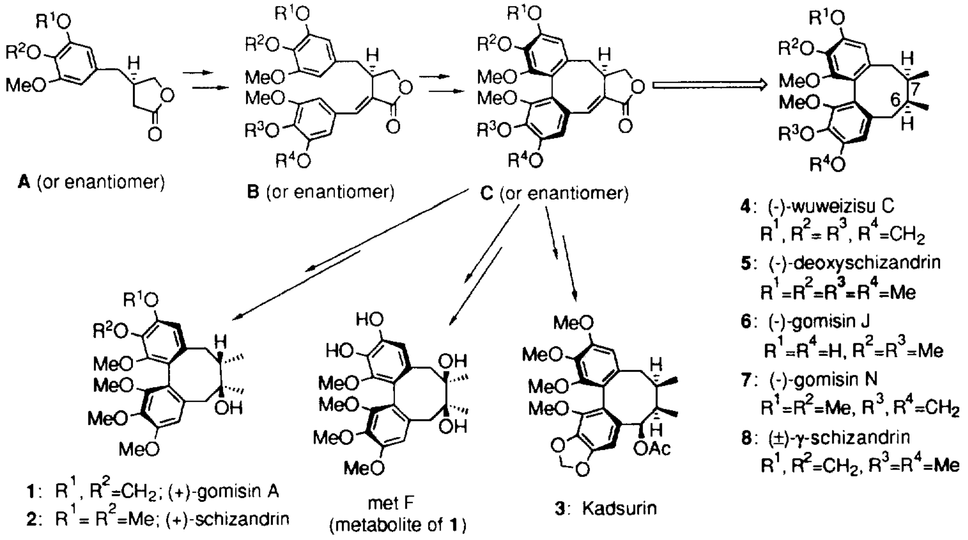
Total Syntheses of the Lignans Isolated from *Schisandra Chinensis*

Masahide Tanaka,* Toshihiro Ohshima, Hiroshi Mitsuhashi, Masao Maruno,
and Takeshi Wakamatsu*

Central Research Laboratories, Tsumura & Co.
Yoshiwara, Ami-machi, Inashiki-gun, Ibaraki 300-11, Japan

Abstract: The total syntheses of wuweizisu C (**4**), gomisin J (**6**), gomisin N (**7**), and γ-schizandrin (**8**) having natural configuration were accomplished in a stereoselective manner. The catalytic hydrogenation or the metal mediated 1,4-reduction of the tetracyclic lactones (**12**, **17**, **22**, **30**) played the significant role for the stereoselective introduction of C6, C7 dimethyl moiety. Furthermore, the neighboring carbonyl group assisted regioselective demethylation of **5** was essential for the synthesis of **6**.

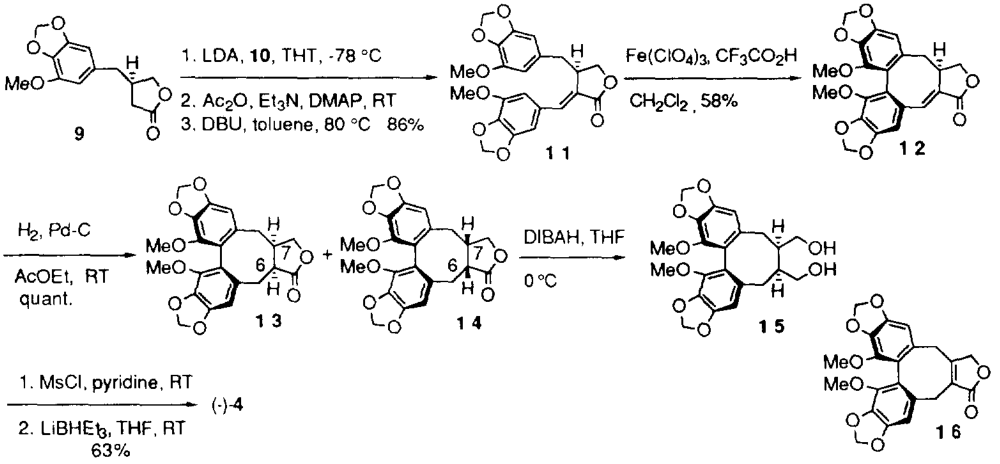
The kernel of *Schisandra chinensis*, which is an important constituent of the Chinese traditional medicine, contains a wide variety of biologically active dibenzocyclooctene lignans.[1] We have been engaged in the research directed to the total synthesis of those natural lignans utilizing the tetracyclic lactones (**C**),[2,5] which were readily available in both enantiomers starting from homochiral butyrolactones (**A**).[2,4] As illustrated in Scheme 1, this strategy has lead to the successful syntheses of a wide variety of dibenzocyclooctene lignans (gomisin A (**1**),[2a,c] schizandrin (**2**),[2a,c] kadsurin (**3**),[2c] and the metabolites of **1**[2d]) in optically pure form. In this paper, we describe the applications of this strategy for the total syntheses of wuweizisu C (**4**),[1a] gomisin J (**6**),[1b] gomisin N(**7**),[1d] and γ-schizandrin (**8**)[1c] in detail.[5]



Scheme 1. Strategy for the total syntheses of dibenzocyclooctene lignans.

Total synthesis of wuweizisu C

The synthesis of **4** was achieved starting from optically pure **9** essentially according to the route reported by Robin and co-workers[3f] for the synthesis of (±)-5 (Scheme 2).[2] Aldol condensation of **9** with 3-methoxy-4,5-(methylenedioxy)benzaldehyde (**10**) to **11** followed by the oxidative coupling with iron perchlorate[6] gave desired biphenyl lactone (**12**) in 50% overall yield as an only isolable product. The observed regioselectivity of the coupling reaction is in good accord with the previous results.[2a,c,d,e,6] The catalytic hydrogenation of the double bond of **12** proceeded stereoselectively affording a mixture of *cis* lactones (**13**, **14**). The *cis* relationship between C6 and C7 position was confirmed by the fact that both **13** and **14** gave a single diol (**15**) by the reduction of lactone moiety. The formation of **14** is the result of palladium catalyzed isomerization of **12** to **16** followed by the hydrogenation of **16**.[3f] Methanesulfonylation of **15** followed by the lithium triethylborohydride reduction afforded optically pure (-)-**4**. The physical data of synthetic **4** were identical with those of natural product.[1a]



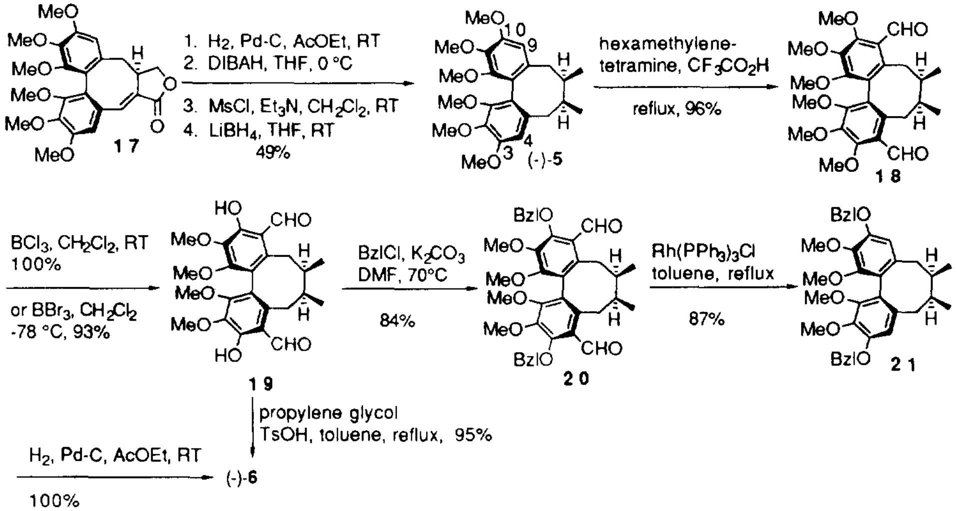
Scheme 2. Total synthesis of wuweizisu C.

Total synthesis of gomisin J

(-)-**6** is a 3,10-*bis*-demethylated product of (-)-deoxyschizandrin (**5**). Thus, we synthesized (-)-(**5**) from (+)-(**17**)[2a,c,e] according to the previously reported method (Scheme 3),[3f,5a] and the demethylation of **5** was attempted. However, it was soon turned out that the attempt to demethylate **5** at the intended position (C3 and C10 position) was not straightforward. In fact, the treatment of **5** with boron tribromide afforded a complex mixture of a variety of mono- and polydemethylated products, in which **6** could not be detected.

The introduction of formyl groups at C4 and C9 positions of (-)-**5** was attempted because the chelation of the Lewis acid to C3-methoxyl and C4-formyl group (C10-methoxyl and C9-formyl at the same time) was expected to activate the C3-methoxyl group (C10-methoxyl group at the same time) for the demethylation reaction.[7] By the Duff reaction, **5** was converted into **18** in 96% yield (Scheme 3). The intended demethylation was carried out on **18** at -78 °C with boron tribromide as a Lewis acid. In the presence of the adjacent formyl groups, the regioselectivity of the demethylation was completely controlled as intended, and the desired demethylated product (**19**) was obtained in 93% yield. More conveniently, demethylation of **18** was achieved with boron trichloride at room temperature affording **19** quantitatively. With the demethylation of the intended position accomplished, the formyl groups finished their role and must be removed. After benzylation of the phenolic hydroxyl groups of **19**, the product (**20**) was deformylated with stoichiometric amount of tris(triphenylphosphine)rhodium chloride in refluxing toluene affording gomisin J dibenzyl ether (**21**) in 87% yield. Catalytic debenzylation of **21** then afforded (-)-**6** quantitatively. Although the spectral data of synthetic **6** were identical with those of natural product, the optical rotation ($[\alpha]_D^{27}$ -96.33°) of the synthetic material was much larger than the reported value for natural **6** ($[\alpha]_D^{24}$ -43.9°).[1b] Then, Dr. Ikeya informed us that the natural **6** is not optically pure but occurs as an enantiomeric mixture of 50-70% e.e.[8] With this information, we confirmed that we have accomplished the total synthesis of optically pure (-)-**6**.

In spite of this successful synthesis, we were not satisfied because the final deformylation steps required the tedious protection-deprotection operations and the use of the stoichiometric amount of expensive rhodium reagent. Therefore, we attempted the direct deformylation method using the retro-Friedel-Crafts reaction, which were known to occur with electron rich aromatic compounds under the acidic and protic conditions.[9] In the event, the treatment of **19** with propylene glycol in the presence of *p*-toluenesulfonic acid in refluxing toluene effected the desired deformylation of **19** affording (-)-**6** in 95% yield.



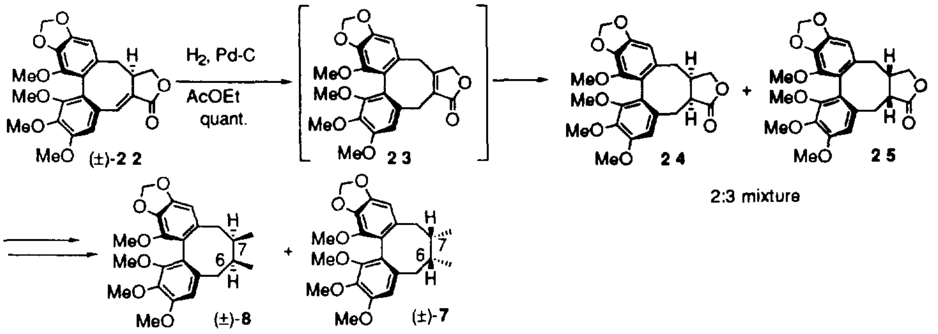
Scheme 3. Total synthesis of gomisin J

Total synthesis of (-)-gomisin N and (±)-γ-schizandrin.

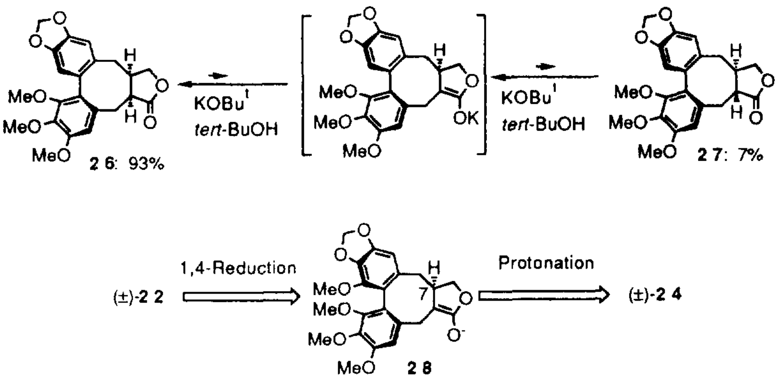
Although the syntheses of (±)-**4** and (±)-**5** have been reported by several groups,[3a-f] the syntheses of the structurally closely related lignans gomisin N (**7**) or γ-schizandrin (**8**) still remains unattained. Probably, this is because the methodologies utilized for the syntheses of **4** or **5** could not be applied for the stereoselective syntheses of **7** or **8**.[3a-f] The brief survey of the structures of **7** and **8** reveals that they are diastereomeric each other, *i.e.*, **8** (occurs in racemic form) possesses the 6*S**, 7*R**, *S**-Biar configurations, while **7** possesses 6*R*, 7*S*, *S*-Biar ones. For the synthetic routes which were employed in the total synthesis of **4** or **5**,[3a-f] it seems difficult to introduce the C6 and C7 stereocenters stereoselectively, and those methodologies would lead to the mixture of **7** and **8**.

For example, by the sequence of the reactions we described above for the synthesis of (-)-**4**, (±)-**22** could be led to the compounds having relative *cis* dimethyl relationship at C6 and C7 position (Scheme 4). However, the control of the absolute configurations at both positions could not be attained due to the intermediacy of the double bond migrated compound (**23**). Consequently, the attempt to synthesize (±)-**8** from (±)-**22** result in the production of the mixture of **7** and **8**.

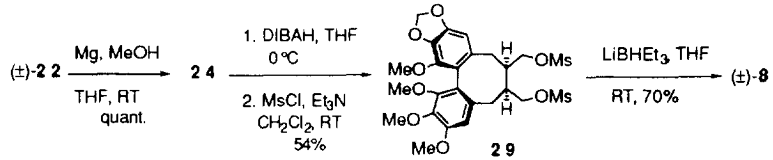
To avoid this undesired double bond migration, the reduction of the double bond must be carried out by the method other than the catalytic hydrogenation. Koga and co-workers have reported that, under the basic condition, the equilibrium between the *cis* and *trans* isomer of the tetracyclic lactones (**26** and **27**) is favorable to the *cis* isomer (Scheme 5).[10] Encouraged with this report, we expected that the enolate (**28**) produced by the 1,4-reduction of **22** would lead to the *cis* product (**24**) predominantly after the protonation, and that the configuration of C7 position would be retained during the reaction because the double bond migration could not be the side reaction in the 1,4-reduction condition.



Scheme 4. Nonstereoselective syntheses of gomisin N and γ-schizandrin.



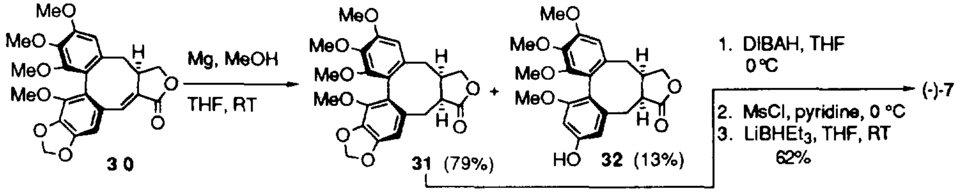
Scheme 5.



Scheme 6. Stereoselective total synthesis of γ-schizandrin.

The desired 1,4-reduction was achieved in methanol using magnesium metal[11] as a reducing reagent. In contrast to the palladium catalyzed hydrogenation, magnesium reduction of **22** afforded the single lactone (**24**) stereoselectively (Scheme 6). To our delight, possible isomer with *trans* ring juncture could not be detected in the reaction mixture. Then, the transformation of lactone ring to dimethyl groups was achieved uneventfully. DIBAH reduction followed by methanesulfonylation afforded dimesylate (**29**), which was reduced with lithium triethylborohydride providing (±)-**8** as a single isomer. The physical data of synthetic **8** were identical with those of natural product.[1c]

The synthesis of (-)-**7** was achieved in an identical manner. The reduction of the known lactone (**30**)[2e] with magnesium afforded the desired product (**31**) as the major one and the phenolic byproduct (**32**) (Scheme 7).[12] Finally, the aforementioned transformation of lactone ring to dimethyl groups furnished (-)-**7** uneventfully. The physical data of synthetic **7** were identical with those of natural product, and the careful inspection of ^{1}H-NMR spectrum assured the absence of γ-schizandrin (**8**), the diastereomer of **7**.[1d]



Scheme 7. Stereoselective total synthesis of gomisin N.

Experimental[14]

(*R*)-3-(5-Methoxy-3,4-methylenedioxybenzyl)butanolide (9). **9** was prepared from (*E*)-3-methoxycarbonyl-4-[5-methoxy-3,4-(methylenedioxy)phenyl]but-3-enoic acid according to the procedure described for the (-)-enantiomer.[2a,c] mp 88-89 °C (colorless prisms from AcOEt). $[\alpha]_D^{23}$ +7.12° (c 1.095, $CHCl_3$). NMR δ: 2.45 (1H, dd, J = 6, 17 Hz), 2.55-2.70 (3H, m), 2.74-2.88 (1H, m), 3.90 (3H, s), 4.03 (1H, dd, J = 5.5, 9 Hz), 4.34 (1H, dd, J = 6.7, 9 Hz), 5.95 (2H, s), 6.30 (1H, d, J = 1.5 Hz), 6.34 (1H, d, J = 1.5 Hz). IR (KBr): 1782, 1632 cm^{-1}. MS m/z: 250 (M$^+$). Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.36; H, 5.76.

(*R*)-(*E*)-2-[5-Methoxy-3,4-(methylenedioxy)benzylidene]-3-[5-methoxy-3,4-(methylenedioxy)benzyl]butanolide (11). To solution of diisopropylamine (1.4 ml, 9.8 mmol) in THF (10 ml) at -70 °C was added *n*-BuLi (1.66 M in hexane, 5.9 ml, 9.8 mmol). Stirring at -70 °C was continued for 10 min, followed by the addition of **9** (1.41 g, 5.6 mmol) in THF (10 ml). The resultant solution was stirred at -70 °C for 30 min, followed by the addition of **10** (1.55 g, 8.6 mmol) in THF (20 ml). The resultant solution was stirred at -70 °C for 5 min. The reaction was quenched with a saturated NH_4Cl and extracted with AcOEt. The combined extracts were washed successively with 2N HCl, water, saturated $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 (20 ml). Et_3N (2 ml), Ac_2O (1.3 ml), and DMAP (100 mg) were added, and the resultant solution was stirred at room temperature for 23 h. The reaction mixture was washed successively with 2N HCl, water, saturated $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$. After evaporation of the solvent, the residue was dissolved in toluene (30 ml), and DBU (2.5 ml) was added. The resultant solution was stirred at 70 °C for 1 h. The reaction mixture was dissolved in AcOEt and washed successively with 2N HCl, water, saturated $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed (AcOEt-hexane 1:2) to afford **11** as a pale yellow solid (2.0g, 86%). mp 125-126 °C (pale yellow prisms from AcOEt-hexane). $[\alpha]_D^{26}$ -97.6° (c 0.54, $CHCl_3$). NMR δ: 2.59 (1H, dd, J = 10, 14 Hz), 2.98 (1H, dd, J = 5, 14 Hz), 3.70-3.84 (1H, m), 3.89 (3H, s), 3.93 (3H, s), 4.28 (2H, d, J = 4 Hz), 5.94 (2H, s), 6.05 (2H, s), 6.33 (1H, d, J = 1.5 Hz), 6.37 (1H, d, J = 1.5 Hz), 6.71 (1H, d, J = 1.2 Hz), 6.77 (1H, d, J = 1.2 Hz), 7.47 (1H, d, J = 1.7 Hz). IR (KBr): 2984, 2944, 1738, 1632, 1602 cm^{-1}. MS m/z: 412 (M$^+$). Anal. Calcd for $C_{22}H_{20}O_8$: C, 64.07; H, 4.89. Found: C, 63.80; H, 5.09.

(3a*R*,*S*-Biar)-3a,4-Dihydro-8,9-dimethoxy-6,7,10,11-bis(methylenedioxy)dibenzo[4,5:6,7]-cycloocta[1,2-*c*]furan-1(3*H*)-one (12). A mixture of **11** (4.06 g, 9.9 mmol), $Fe(ClO_4)_3 \cdot 6H_2O$ (10.5 g, 22.7 mmol), and CF_3CO_2H (20 ml) in CH_2Cl_2 (200 ml) was stirred at room temperature for 4.5 h. AcOEt was added, and the organic layer was washed with 2N HCl, water, saturated $NaHCO_3$, brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed (CH_2Cl_2) to give **12** as a colorless solid (2.33 g, 58%). mp 258-260 °C (colorless prisms from AcOEt-hexane). $[\alpha]_D^{26}$ +439° (c 0.335, $CHCl_3$). NMR δ: 2.39 (1H, dd, J = 1.5, 14 Hz), 2.98 (1H, dd, J = 7, 14 Hz), 3.39-3.55 (1H, m), 3.81 (3H, s), 3.86 (3H, s), 4.08 (1H, dd, J = 9, 10 Hz), 4.43 (1H, t, J = 9 Hz), 5.95 (1H, d, J = 1.5 Hz), 5.97 (1H, d, J = 1.5

Hz), 6.02 (2H, s), 6.47 (1H, d, J = 0.7 Hz), 6.34 (1H, s), 7.45 (1H, d, J = 3.7 Hz). IR (KBr): 2972, 1752, 1672, 1620 cm^{-1}. MS m/z: 410 (M$^+$). Anal. Calcd for $C_{22}H_{18}O_8$: C, 64.39; H, 4.42. Found: C, 64.27; H, 4.68.

(3a*R*,13a*S*,*S*-Biar)-3a,4,13,13a-Tetrahydro-8,9-dimethoxy-6,7,10,11-bis(methylenedioxy)-dibenzo[4,5:6,7]cycloocta[1,2-*c*]furan-1(3*H*)-one (13) and (3a*S*,13a*R*,*S*-Biar)-3a,4,13,13a-Tetrahydro-8,9-dimethoxy-6,7,10,11-bis(methylenedioxy)dibenzo[4,5:6,7]cycloocta[1,2-*c*]-furan-1(3*H*)-one (14). **12** (49 mg, 0.12 mmol) was hydrogenated over 10% Pd-C (23 mg) in AcOEt (2 ml) under a hydrogen atmosphere at room temperature for 70.5 h. The catalyst was filtered off, and the filtrate was concentrated to give an inseparable mixture of **13** and **14** as a colorless oil (55 mg, 100%). NMR δ: 2.40-2.52 (4H, m), 2.88-3.01 (1H, m), 3.15 (1H, dd, J = 7, 15 Hz), 3.86 (3H, s), 3.91 (3H, s), 4.04 (1H, t, J = 9 Hz), 4.40 (1H, dd, J = 7, 9 Hz), 5.93-6.04 (4H, m), 6.32 (0.3H, s), 6.53 (0.7H, s), 6.66 (0.3H, s), 6.96 (0.7H, s).

(6*S*,7*R*,*S*-Biar)-5,6,7,8-Tetrahydro-6,7-bis(hydroxymethyl)-1,12-dimethoxy-2,3,10,11-bis(methylenedioxy)dibenzo[*a*,*c*]cyclooctene (15). DIBAH (1.5 M in toluene, 1.0 ml, 1.5 mmol) was added to a solution of a mixture of **13** and **14** (55 mg, 0.12 mmol) in THF (2 ml) at 0 °C. The resultant solution was stirred at 0 °C for 15 min, and the reaction was quenched with $Na_2SO_4 \cdot 10H_2O$. After the filtration of the insoluble material, the filtrate was evaporated to afford **15** as a colorless amorphous solid (61 mg, 100%). $[\alpha]_D^{26}$ -43.8° (c 0.365, $CHCl_3$). NMR δ: 1.80-2.28 (6H, m), 2.39 (1H, dd, J = 2, 14 Hz), 2.82 (1H, dd, J = 8, 14 Hz), 3.48 (1H, dd, J = 7, 11 Hz), 3.65 (1H, d, J = 7 Hz), 3.83 (3H, s), 3.84 (3H, s), 3.71-3.93 (2H, m), 5.93-6.00 (4H, m), 6.48 (1H, s), 6.58 (1H, s). IR ($CHCl_3$): 3620, 3408, 2944, 1618 cm^{-1}. MS m/z: 416 (M$^+$). HRMS m/z: Calcd for $C_{22}H_{24}O_8$ (M$^+$): 416.14712. Found: 416.14770.

(-)-Wuweizisu C (4). Methanesulfonyl chloride (1.0 ml) was added to a solution of **15** (1.50 g, 3.61 mmol) in pyridine (2 ml), and the resultant mixture was stirred at room temperature for 3 h. AcOEt was added, and the organic layer was washed successively with 2N HCl, water, saturated $NaHCO_3$, brine, and dried over $MgSO_4$. After evaporation of the solvent, mesylate of **15** was obtained as a colorless amorphous solid (1.9 g, 92%). To a solution of the mesylate of **15** (55 mg, 0.096 mmol) in THF (2 ml) was added $LiBHEt_3$ (1.0 M in THF, 1 ml, 1 mmol), and the resultant solution was stirred at room temperature for 2 h. The reaction was quenched with acetone. After addition of AcOEt, the organic layer was washed successively with 2N HCl, water, brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed (AcOEt-hexane 1:2) to give (-)-**4** as a colorless solid (25 mg, 68%). mp 115-117 °C (colorless plates from MeOH). $[\alpha]_D^{28}$ -59.2° (c 0.29, $CHCl_3$). NMR δ: 0.72 (3H, d, J = 7 Hz), 0.95 (3H, d, J = 7 Hz), 1.60-1.98 (2H, m), 1.99 (1H, d, J = 13 Hz), 2.24 (1H, dd, J = 9, 13 Hz), 2.44 (1H, dd, J = 2, 13 Hz), 2.54 (1H, dd, J = 13, 7 Hz), 5.933 (1H, d, J = 1.5 Hz), 5.94 (1H, d, J = 1.5 Hz), 5.94 (1H, d, J = 1.5 Hz), 5.96 (1H, d, J = 1.5 Hz), 6.476 (1H, s), 6.48 (1H, s). IR (KBr): 2952, 1616, 1472 cm^{-1}. MS m/z: 384 (M$^+$). Anal. Calcd for $C_{22}H_{24}O_6$: C, 68.73; H, 6.29. Found: C, 68.53; H, 6.41.

(3a*R*,*S*-Biar)-3a,4-Dihydro-6,7,8,9,10,11-hexamethoxydibenzo[4,5:6,7]cycloocta[1,2-*c*]-furan-1(3*H*)-one (17). **17** was prepared from (*R*)-3-(3,4,5-trimethoxybenzyl)butyrolactone[2e] according to the procedure described for the (-)-enantiomer.[2a,c] $[\alpha]_D^{26}$ +279° (c 1.01, $CHCl_3$). NMR δ: 2.46 (1H, dd, J = 1, 14 Hz), 3.06 (1H, dd, J = 6.6, 14 Hz), 3.43-3.59 (1H, m), 3.59 (3H, s), 3.64 (3H, s), 3.88 (3H, s), 3.89 (3H, s), 3.90 (3H, s), 3.91 (3H, s), 4.10 (1H, dd, J = 9, 10 Hz), 4.47 (1H, t, J = 9 Hz), 6.59 (1H, s), 6.41 (1H, s), 7.53 (1H, d, J = 3 Hz). IR ($CHCl_3$): 2940, 2840, 1756, 1674, 1596 cm^{-1}. MS m/z: 442 (M$^+$). HRMS m/z: Calcd for $C_{24}H_{26}O_8$ (M$^+$): 442.16279. Found: 442.16279

(-)-Deoxyschizandrin (5). **5** was prepared from **17** (49% overall) as described for the synthesis of **4** from **12**. mp 84-87 °C (colorless plates from Et_2O-hexane). $[\alpha]_D^{25}$ -108.6° (c 0.965, $CHCl_3$). NMR δ: 0.74 (3H, d, J = 7 Hz), 1.00 (3H, d, J = 7 Hz), 1.79-1.83 (1H, m), 1.88-1.93 (1H, m), 2.05 (1H, dd, J = 1, 13 Hz), 2.28 (1H, dd, J = 10, 13 Hz), 2.50 (1H, dd, J = 2, 14 Hz), 2.58 (1H, dd, J = 7, 14 Hz), 3.58 (3H, s), 3.59 (3H, s), 3.87 (3H, s), 3.88 (3H, s), 3.89 (3H, s), 3.90 (3H, s), 6.53 (1H, s), 6.54 (1H, s). IR (KBr): 2940, 1594, 1488 cm^{-1}.

(6*S*,7*R*,*S*-Biar)-5,6,7,8-Tetrahydro-6,7-dimethyl-1,2,3,10,11,12-hexamethoxydibenzo[*a*,*c*]-cyclooctene-4,9-dicarbaldehyde (18). A solution of **5** (1.0 g) and hexamethylenetetramine (2.5 g) in CF_3CO_2H (25 ml) was heated under reflux for 24 h. Water was added and the resultant mixture was stirred at room temperature for 3 days. AcOEt was added, and the organic layer was washed with saturated $NaHCO_3$ and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed (AcOEt-hexane 1:5) to give **18** as a colorless solid (1.092 g, 96%). mp 108-109 °C (colorless prisms from Et_2O-hexane). $[\alpha]_D^{27}$ +223° (c 0.69, $CHCl_3$). NMR δ: 0.77 (3H, d, J = 7 Hz), 1.09 (3H, d, J = 7 Hz), 1.63-1.80 (1H, m), 1.85-2.15 (4H, m), 2.98 (1H, d, J = 12 Hz), 3.63 (3H, s), 3.72 (3H, s), 3.90 (3H, s), 3.92 (3H, s), 4.04 (3H, s), 4.06 (3H, s), 10.50 (1H, s), 10.52 (1H, s). IR (KBr): 2936, 1680, 1562 cm^{-1}. MS m/z: 472 (M$^+$). HRMS m/z: Calcd for $C_{26}H_{32}O_8$ (M$^+$): 472.20972. Found: 472.21178.

(6*S*,7*R*,*S*-Biar)-5,6,7,8-Tetrahydro-3,10-dihydroxy-6,7-dimethyl-1,2,11,12-tetramethoxy-dibenzo[*a*,*c*]cyclooctene-4,9-dicarbaldehyde (19). A) At -78 °C, BBr_3 (1.0 M in CH_2Cl_2, 0.5 ml, 0.5 mmol) was added to a solution of **18** (100 mg, 0.21 mmol) in CH_2Cl_2 (10 ml), and the solution was stirred at -78 °C for 10 min. Saturated $NaHCO_3$ was added to the reaction mixture and the organic layer was separated and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed (AcOEt-hexane 1:4) to give **19** as a colorless oil (87 mg, 93%).

B) BCl_3 (1.0 M in CH_2Cl_2, 1.1 ml, 1.1 mmol) was added to a solution of **18** (209 mg, 0.443 mmol) in CH_2Cl_2 (20 ml), and the solution was stirred at 0 °C for 18 h. Saturated $NaHCO_3$ was added to the reaction mixture and the organic layer was separated and dried over $MgSO_4$. After evaporation of the solvent, **19** was obtained as a colorless oil (204 mg, 100%). $[\alpha]_D^{24}$ +234° (c 0.255, $CHCl_3$). NMR δ: 0.69 (3H, d, J = 7 Hz), 1.05 (3H, d, J = 7 Hz), 1.76-1.94 (1H, m), 2.00-2.20 (1H, m), 2.16 (1H, dd, J = 9, 15 Hz), 2.45 (1H, d, J = 15 Hz), 2.62 (1H, d, J = 15 Hz), 3.38 (1H, dd, J = 9, 15 Hz), 3.83 (3H, s), 3.81 (3H, s), 3.90 (3H, s), 3.93 (3H, s), 10.19 (1H, s), 10.34 (1H, s), 12.72 (1H, s), 12.85 (1H, s). IR ($CHCl_3$): 3600, 2960, 1630, 1572 cm^{-1}. MS m/z: 444 (M$^+$). HRMS m/z: Calcd for $C_{24}H_{28}O_8$ (M$^+$): 444.17842. Found: 444.17843.

(6*S*,7*R*,*S*-Biar)-3,10-Dibenzyloxy-5,6,7,8-tetrahydro-6,7-dimethyl-1,2,11,12-tetramethoxy-dibenzo[*a*,*c*]cyclooctene-4,9-dicarbaldehyde (20). A mixture of **19** (73.3 mg, 0.165 mmol), K_2CO_3 (138 mg, 1 mmol), and benzyl bromide (0.1 ml, 0.84 mmol) in DMF (3 ml) was heated at 70 °C for 5 h. AcOEt was added, and the organic layer was washed with 2N HCl, water, saturated $NaHCO_3$, and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed (AcOEt-hexane 1:5) to give **20** as a colorless oil (86 mg, 84%). $[\alpha]_D^{27}$ +166.6° (c 0.470, $CHCl_3$). NMR δ: 0.48 (3H, d, J = 7 Hz), 1.05 (3H, d, J = 7 Hz), 1.52-1.75 (2H, m), 1.90-2.18 (3H, m), 2.97 (1H, d, J = 12 Hz), 3.62 (3H, s), 3.71 (3H, s), 3.92 (3H, s), 3.94 (3H, s), 5.24 (2H, s), 5.21 (1H, d, J = 11 Hz), 5.29 (1H, d, J = 11 Hz), 7.22-7.53 (10H, m), 10.42 (1H, s), 10.46 (1H, s). IR (KBr): 3004, 2940, 1680, 1560 cm^{-1}. MS m/z: 624 (M$^+$). HRMS m/z: Calcd for $C_{38}H_{40}O_8$ (M$^+$): 624.27232. Found: 624.27091.

(6*S*,7*R*,*S*-Biar)-3,10-Dibenzyloxy-5,6,7,8-tetrahydro-6,7-dimethyl-1,2,11,12-tetramethoxy-dibenzo[*a*,*c*]cyclooctene (21). A solution of **20** (68 mg, 0.11 mmol) and $Rh(PPh_3)_3Cl$ (250 mg, 0.27 mmol) in toluene (5 ml) was heated under reflux for 2 days. The insoluble material was filtered off, and the filtrate was concentrated. The residue was chromatographed (AcOEt-hexane 1:4) to give **21** (54 mg, 87%) as a colorless oil. $[\alpha]_D^{24}$ -70.94° (c 0.265, $CHCl_3$). NMR δ: 0.59 (3H, d, J = 7 Hz), 0.75 (3H, d, J = 7 Hz), 1.60-1.90 (2H, m), 2.01 (1H, d, J = 14 Hz), 2.24 (1H, dd, J = 9, 14 Hz), 2.44 (1H, dd, J = 3, 14 Hz), 2.53 (1H, dd, J = 7, 14 Hz), 3.606 (3H, s), 3.611 (3H, s), 3.89 (3H, s), 3.91 (3H, s), 5.13 (2H, s), 5.13 (1H, d, J = 12 Hz), 5.19 (1H, d, J = 12 Hz), 6.57 (1H, s), 6.61 (1H, s), 7.25-7.52 (10H, m). IR (KBr): 2960, 2932, 1596 cm^{-1}. MS m/z: 568 (M$^+$). HRMS m/z: Calcd for $C_{36}H_{40}O_6$ (M$^+$): 568.28249. Found: 568.28220.

(-)-Gomisin J (6). A) A solution of **21** (45 mg) in AcOEt (5 ml) containing 10% Pd-C (10 mg) was stirred at room temperature under a hydrogen atmosphere for 2 h. The catalyst was filtered off, and the filtrate was concentrated to give **6** as a colorless solid (33 mg, 100%).

B) A solution of **19** (479 mg, 1.08 mmol), propylene glycol (0.85 ml, 11.7 mmol), and *p*-toluenesulfonic acid

(200 mg, 1.05 mmol) in toluene (20 ml) was heated under reflux for 1.5 h. AcOEt was added, and the organic layer was washed with saturated $NaHCO_3$, and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed (AcOEt-hexane 1:2) to give **6** as a colorless solid (399 mg, 95%). mp 125-126.0 °C (colorless needles from MeOH-H_2O). $[\alpha]_D^{27}$ -96.33° (c 0.545, $CHCl_3$). NMR δ: 0.73 (3H, d, J = 7 Hz), 0.97 (3H, d, J = 7 Hz), 1.68-1.95 (2H, m), 2.05 (1H, d, J = 15 Hz), 2.24 (1H, dd, J = 9, 14 Hz), 2.45 (1H, dd, J = 15, 2 Hz), 2.54 (1H, dd, J = 8, 14 Hz), 3.52 (6H, s), 3.92 (3H, s), 3.93 (3H, s), 5.70 (1H, s), 5.73 (1H, s), 6.63 (2H, s). IR (KBr): 3412, 2932, 2872, 1584 cm^{-1}.

(3a*RS*,*SR*-Biar)-3a,4-Dihydro-8,9,10,11-tetramethoxy-6,7-(methylenedioxy)dibenzo[4,5:6,7]cycloocta[1,2-*c*]furan-1(3*H*)-one (22). **22** was prepared from (±)-3-[5-methoxy-3,4-(methylenedioxy)benzyl]butyrolactone[13] according to the procedure described for (-)-enantiomer.[2a,c] mp 189-190 °C (colorless needles from AcOEt-hexane). NMR δ: 2.42 (1H, dd, J = 1.5, 14 Hz), 3.00 (1H, dd, J = 7, 14 Hz), 3.42-3.60 (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 (1H, s), 7.51 (1H, d, J = 2 Hz). IR ($CHCl_3$): 2964, 2940, 1754, 1674, 1620 cm^{-1}. MS m/z: 426 (M^+). Anal. Calcd for $C_{23}H_{22}O_8$: C, 64.78; H, 5.20. Found: C, 64.45; H, 5.08.

(±)-γ-Schizandrin (8) and (±)-Gomisin N (7). A mixture of (±)-**8** and (±)-**7** was prepared from (±)-**22** (58% overall) as described for the synthesis of **4** from **12**. NMR δ: 0.73 (3H, d, J = 7 Hz), 0.97 (1.8H, d, J = 7 Hz), 0.99 (1.2H, d, J = 7 Hz), 1.70-2.06 (2H, m), 2.10-2.30 (2H, m), 2.40-4.64 (2H, m), 3.53 (1.2H, s), 3.54 (1.8H, s), 3.82 (1.8H, s), 3.83 (1.2H, s), 3.90 (3H, s), 3.91 (3H, s), 5.96 (2H, s), 6.49 (1H, s), 6.76 (1H, s).

(3a*RS*,13a*SR*,*SR*-Biar)-3a,4,13,13a-Tetrahydro-8,9,10,11-tetramethoxy-6,7-(methylenedioxy)dibenzo[4,5:6,7]cycloocta[1,2-*c*]furan-1(3*H*)-one (24). To a solution of **22** (50 mg, 0.12 mmol) in MeOH (8 ml) and THF (2 ml) was added Mg (300 mg, 12.3 mmol) and the resultant mixture was stirred at room temperature for 5 h. AcOEt was added, and the organic layer was washed with 2N HCl, water, saturated $NaHCO_3$, and dried over $MgSO_4$. After evaporation of the solvent, **24** was obtained as a colorless solid (51 mg, 100%). mp 229-230 °C (colorless needles from AcOEt). NMR δ: 2.47-2.95 (6H, m), 3.65 (3H, s), 3.87 (3H, s), 3.89 (3H, s), 3.90 (3H, s), 4.11 (1H, dd, J = 9, 12 Hz), 4.40 (1H, t, J = 9 Hz), 5.99 (2H, s), 6.30 (1H, s), 6.73 (1H, s). IR (KBr): 2928, 1746, 1618, 1600 cm^{-1}. MS m/z: 428 (M^+). Anal. Calcd for $C_{23}H_{24}O_8 \cdot 1/5H_2O$: C, 63.94; H, 5.69. Found: C, 64.04; H, 5.65.

(6*RS*,7*SR*,*RS*-Biar)-5,6,7,8-Tetrahydro-6,7-bis(methanesulfonyloxymethyl)-1,2,3,12-tetramethoxy-10,11-(methylenedioxy)dibenzo[*a*,*c*]cyclooctene (29). DIBAH (1.5 M in toluene, 3.0 ml, 4.5 mmol) was added to a solution of **24** (427 mg, 1.0 mmol) in THF (10 ml) at 0 °C. The resultant solution was stirred at 0 °C for 1 h, and the reaction was quenched with $Na_2SO_4 \cdot 10H_2O$. The insoluble material was filtered off, and the evaporation of the filtrate afforded a colorless amorphous solid (344 mg). To a solution of this solid (344 mg) in CH_2Cl_2 (5 ml) were added methanesulfonyl chloride (0.2 ml, 2.6 mmol) and Et_3N (0.5 ml, 3.5 mmol), and the resultant mixture was stirred at room temperature for 1.5 h. AcOEt was added, and the organic layer was washed successively with 2N HCl, water, saturated $NaHCO_3$, brine, and dried over $MgSO_4$. After evaporation of the solvent, **29** was obtained as a colorless amorphous solid (316 mg, 54%). NMR δ: 2.06-2.50 (5H, m), 2.90 (1H, dd, J = 8, 14 Hz), 3.05 (3H, s), 3.08 (3H, s), 3.58 (3H, s), 3.84 (3H, s), 3.88 (3H, s), 3.90 (3H, s), 4.10-4.30 (4H, m), 5.98 (1H, d, J = 1.5 Hz), 5.99 (1H, d, J = 1.5 Hz), 6.58 (1H, s), 6.59 (1H, s). IR ($CHCl_3$): 3008, 2940, 1620, 1598 cm^{-1}. MS m/z: 588 (M^+). HRMS m/z: Calcd for $C_{25}H_{32}S_2O_{12}$ (M^+): 588.13352. Found: 588.13289.

(±)-γ-Schizandrin (8). To a solution of **29** (285 mg, 0.48 mmol) in THF (5 ml) was added $LiBHEt_3$ (1.0 M in THF, 5 ml, 5 mmol). The resultant solution was stirred at room temperature for 63 h, and the reaction was quenched with acetone. After addition of AcOEt, the organic layer was washed successively with 2N HCl, water, brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed (AcOEt-hexane 1:9) to give **8** as a colorless solid (136 mg, 70%). mp 128-129.5 °C (colorless needles from AcOEt-hexane). NMR δ: 0.73 (3H, d, J = 7 Hz), 0.99 (3H, d, J = 7 Hz), 1.77-1.81 (1H, m), 1.87-1.91 (1H, m), 2.03 (1H, d, J = 13 Hz), 2.30 (1H, dd, J = 10, 13 Hz), 2.43 (1H, dd, J = 2, 14 Hz), 2.55 (1H, dd, J = 7, 14 Hz), 3.53 (3H, s), 3.82 (3H, s), 3.88 (3H, s), 3.89 (3H, s), 5.94 (1H, d, J = 1.5 Hz), 5.95 (1H, d, J = 1.5 Hz), 6.47 (1H, s), 6.54 (1H, s). IR (KBr): 2956, 2876, 1618, 1596 cm^{-1}. MS m/z: 400 (M$^+$).

(3a*R*,13a*S*,*S*-Biar)-3a,4,13,13a-Tetrahydro-6,7,8,9-tetramethoxy-10,11-(methylenedioxy)-dibenzo[4,5:6,7]cycloocta[1,2-*c*]furan-1(3*H*)-one (31) and (3a*R*,13a*S*,*S*-Biar)-3a,4,13,13a-Tetrahydro-11-hydroxy-6,7,8,9-tetramethoxydibenzo[4,5:6,7]cycloocta[1,2-*c*]furan-1(3*H*)-one (32). Mg (521 mg) was added to a solution of **30** (105 mg, 0.25 mmol) in THF (5 ml) and MeOH (15 ml), and the mixture was stirred at room temperature for 4 h. 2N HCl was added, and the resultant mixture was extracted with AcOEt. The combined organic layers were washed with 2N HCl, water, saturated $NaHCO_3$, brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed (AcOEt-hexane 2:1) to give **31** as a colorless solid (77.7 mg, 79%) and **32** as a colorless solid (12.4 mg, 13%). **31**: mp 186-188 °C (colorless needles from AcOEt-hexane). $[\alpha]_D^{27}$ +2.2° (c 0.58, $CHCl_3$). NMR δ: 2.40-2.93 (6H, m), 3.63 (3H, s), 3.88 (6H, s), 3.90 (3H, s), 4.11 (1H, dd, J = 9, 12 Hz), 4.40 (1H, t, J = 9 Hz), 5.98 (2H, s), 6.37 (1H, s), 6.65 (1H, s). IR (KBr): 2932, 1766, 1620, 1596 cm^{-1}. MS m/z: 428 (M$^+$). Anal. Calcd for $C_{23}H_{24}O_8$: C, 64.48; H, 5.65. Found: C, 64.30; H, 5.71. **32**: mp 217-219 °C (colorless needles from CH_2Cl_2-hexane). $[\alpha]_D^{28}$ +22.9° (c 0.55, $CHCl_3$). NMR δ: 2.48-3.00 (6H, m), 3.69 (3H, s), 3.73 (3H, s), 3.88 (6H, s), 4.13 (1H, dd, J = 8, 11 Hz), 4.42 (1H, t, J = 8 Hz), 5.48 (1H, s), 6.38 (1H, s), 6.42 (1H, d, J = 2.2 Hz), 6.49 (1H, d, J = 2.2 Hz). IR (KBr): 3436, 2936, 1766, 1594 cm^{-1}. MS m/z: 400 (M$^+$). Anal. Calcd for $C_{22}H_{24}O_7\cdot 1/3H_2O$: C, 65.01; H, 6.12. Found: C, 64.98; H, 6.28.

(-)-Gomisin N (7). **(-)-7** was prepared from **31** (62% overall) as described for the synthesis of **8** from **24**. mp 102-103.5 °C (colorless plates from Et_2O-hexane). $[\alpha]_D^{26}$ -82° (c 0.32, $CHCl_3$). NMR δ: 0.73 (3H, d, J = 7.1 Hz), 0.97 (3H, d, J = 7.2 Hz), 1.74-1.82 (1H, m), 1.85-1.92 (1H, m), 2.02 (1H, dd, J = 1.5, 13.3 Hz), 2.23 (1H, dd, J = 9.5, 13.3 Hz), 2.52 (1H, dd, J = 2.3, 13.7 Hz), 2.57 (1H, dd, J = 7.2, 13.7 Hz), 3.54 (3H, s), 3.81 (3H, s), 3.88 (3H, s), 3.89 (3H, s), 5.94 (1H, d, J = 1.5 Hz), 5.95 (1H, d, J = 1.5 Hz), , 6.47 (1H, s), 6.55 (1H, s). IR (KBr): 2944, 2920, 1620 cm^{-1}. MS m/z: 400 (M$^+$). Anal. Calcd for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05. Found: C, 68.70; H, 7.14.

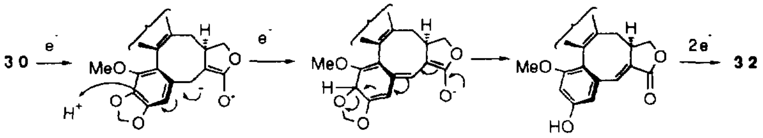
Acknowledgment We are grateful to Dr. Ikeya in our institute for his kind discussions and advice.

REFERENCES AND NOTES

1. Isolations of the natural dibenzocyclooctene lignans: (a) Wuweizisu C: Ikeya, Y.; Taguchi, H.; Yoshioka, I. *Chem. Pharm. Bull.* **1982**, *30*, 3207. (b) Gomisin J: Ikeya, Y.; Taguchi, H.; Yoshioka, I.; Kobayashi, H. *ibid.* **1979**, *27*, 1583. (c) γ-Schizandrin: Ikeya, Y.; Taguchi, H.; Yoshioka, I. *ibid.* **1982**, *30*, 132. (d) Gomisin N; Ikeya, Y.; Taguchi, H.; Yoshioka, I.; Kobayashi, H. *ibid.* **1979**, *27*, 2695, and references cited therein.
2. Gomisin A, schizandrin, and isoschizandrin: (a) Tanaka, M.; Mukaiyama, C.; Mitsuhashi, H.; Wakamatsu, T. *Tetrahedron Lett.* **1992**, *33*, 4165. (b) Tanaka, M.; Itoh, H.; Mitsuhashi, H.; Maruno, M.; Wakamatsu, T. *Tetrahedron Asymmetry* **1993**, *4*, 605. (c) Tanaka, M.; Mukaiyama, C.; Mitsuhashi, H.; Maruno, M.; Wakamatsu, T. *J. Org. Chem.* **1995**, *60*, 4339. Metabolites of gomisin A: (d) Tanaka, M.; Mitsuhashi, H.; Maruno, M.; Wakamatsu, T. *Synlett* **1994**, 604. Kadsurin: (e) Ohshima, T.; Tanaka, M.; Mitsuhashi, H.; Maruno, M.; Wakamatsu, T. *Tetrahedron Asymmetry* **1995**, *6*, 139. This strategy was originally reported by Robin and co-workers for the synthesis of (±)-deoxyschizandrin. See ref. 3f.
3. The syntheses of natural and related dibenzocyclooctenes: Deoxyschizandrin and wuweizisu C: (a) Kochetkov, N. K.; Khorlin, A.; Chizhov, O. S. *Tetrahedron Lett.* **1962**, 361. (b) Ghera, E.; Ben-David, Y. ; Becker, D. *ibid.* **1977**, 463. (c) Biftu, T.; Hazra, B. G.; Stevenson, R. *J. Chem. Soc., Perkin Trans. I* **1979**, 2276. (d) Schneiders, G. E.; Stevenson, R. *J. Org. Chem.* **1981**, *46*, 2969. (e) Takeya, T.; Ohkubo, T.; Nishida, S.; Tobinaga, S. *Chem. Pharm. Bull.* **1985**, *33*, 3599; (f) Landais, Y.; Robin, J. P.; Lebrun, A. *Tetrahedron* **1991**, *47*, 3787. Schizandrin, gomisin A, and

isoschizandrin: (g) Ghera, E.; Ben-David, Y. *J. Chem. Soc., Chem. Commun.* **1978**, 480. (h) Warshawsky, A. M.; Meyers, A. I. *J. Am. Chem. Soc.* **1990**, *112*, 8090. (i) Takeya, T.; Ohguchi, A.; Arai, Y.; Tobinaga, S. *Chem. Pharm. Bull.* **1994**, *42*, 430. (j) Takeya, T.; Ohguchi, A.; Tobinaga, S. *ibid.* **1994**, *42*, 438. Kadsurin: (k) Mervic, M.; Ghera, E. *J. Am. Chem. Soc.* **1977**, *99*, 7673.

4. Morimoto, T.; Chiba, M.; Achiwa, K. *Tetrahedron Lett.* **1989**, *30*, 735. Robin, J. P.; Gringore, O.; Brown, E. *Tetrahedron Lett.*, **1980**, *21*, 2709. Lalami, K.; Dhal, R.; Brown, E. *Heterocycles* **1988**, *27*, 1131. Lalami, K.; Dhal, R.; Brown, E. *J. Nat. Prod.* **1991**, *54*, 119.
5. The preliminary reports have been reported: (a) Tanaka, M.; Mitsuhashi, H.; Maruno, M.; Wakamatsu, T. *Tetrahedron Lett.* **1994**, *35*, 3733. (b) Tanaka, M.; Ohshima, T.; Mitsuhashi, H.; Maruno, M.; Wakamatsu, T. *Heterocycles* **1994**, *37*, 739.
6. Tanaka, M.; Mitsuhashi, H.; Wakamatsu, T. *Tetrahedron Lett.* **1992**, *33*, 4161.
7. Nagaoka, H.; Schmidt, G.; Iio, H.; Kishi, Y. *Tetrahedron Lett.* **1981**, *22*, 899.
8. Ikeya, Y.; Kanatani, H. unpublished result.
9. (a) Grozinger, K.; Hess, F. *Synthesis* **1977**, 411. (b) Smith, K. M.; Miura, M.; Tabba, H. D. *J. Org. Chem.* **1983**, *48*, 4779. (c) Keumi, T.; Morita, T.; Inoue, Y.; Teshima, N.; Kitajima, H. *Synthesis* **1985**, 979.
10. Tomioka, K.; Mizuguchi, H.; Ishiguro, T.; Koga, K. *Chem. Pharm. Bull.* **1985**, *33*, 121.
11. Youn, I. K.; Yon, G. H.; Pak, C. S. *Tetrahedron Lett.* **1986**, *27*, 2409.
12. Compound **32** was produced by the reductive cleavage of methylenedioxy group and subsequent 1,4-reduction of the double bond as shown below.



13. Schneider, G. E.; Stevenson, R. *J. Chem. Soc., Perkin 1* **1982**, 999.
14. 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 (IR) were obtained with a Hitachi 270-30 spectrophotometer. NMR spectra were measured 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 (HRMS) were measured with a KRATOS CONCEPT 32 1H and 1S mass spectrometers. Flash chromatography was performed with silica gel 60 (230-400 mesh).

(*Received in Japan* 10 *July* 1995; *accepted* 29 *August* 1995)