Synthesis of Optically Pure Gomisi Lignans: The Total Synthesis of (+)-Schizandrin, (+)-Gomisin A, and (+)-Isoschizandrin in Naturally Occurring Forms

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The total syntheses of (+)-schizandrin (**1**), (+)-gomisin A (**2**), and (+)-isoschizandrin (**3**) having natural configurations were accomplished. Optically pure butyrolactones ((−)-**9**, (−)-**31**) were transformed to α-benzylidenebutyrolactones ((+)-**10**, (+)-**32**, (+)-**35**). By a highly efficient iron(III) perchlorate-mediated oxidative coupling reaction of **10**, **32**, and **35**, the key intermediates with biphenyl skeletons ((−)-**11**, (−)-**33**) were constructed with high stereoselectivity. Several methods for the stereoselective introduction of the C6-hydroxyl group were examined. For the synthesis of schizandrin and gomisin A, the Mukaiyama hydration reaction of (−)-**11** and (−)-**33** provided the desired products with satisfactory selectivity. For the synthesis of isoschizandrin, the stereoselective epoxidation of allylic alcohol (+)-**48** was successfully utilized taking advantage of its conformational features.

Introduction

The kernel of *Schisandra chinensis*, "gomisi" in Japanese or "wuweizi" in Chinese, is important in Chinese traditional medicine and is used as an antitussive and a tonic.[1] The extensive study of Ikeya and co-workers[2] accomplished the isolation and structure determination of the kernel's components.[2] It has since been revealed that the pharmaceutical properties of the kernel of *S. chinensis* are ascribable to various lignans with the dibenzocyclooctene nucleus, which are related to the well known antineoplastic natural product steganacin.[3] Pharmacologically, most of these lignans were found to display an antihepatotoxic effect, with (+)-gomisin A (**2**) being the most potent.[1] Structurally, the wide variety of dibenzocyclooctene lignans can be categorized into the following three groups: (1) compounds with a C6 hydroxyl group represented by (+)-schizandrin (**1**),[2a,b] (+)-gomisin A (**2**),[2b] and (+)-isoschizandrin (**3**),[2c] in which the configuration of the biphenyl part is *R*; (2) compounds with a C5 hydroxyl group represented by (−)-gomisin O (**4**),[2e] in which the configuration of the biphenyl part is *S*; (3) compounds without a hydroxyl group on the eight-membered ring, such as (+)-deoxyschizandrin (**5**)[2d,e] or (−)-wuweizisu C (**6**),[2f] which occur having *R* or *S* biphenyl configurations.

In spite of the important pharmacological properties of these lignans, attention paid to them by synthetic chemists has been limited. Only a few total syntheses of the simplest representatives, deoxyschizandrin (**5**),[4a–c,e] wuweizisu C (**6**),[4d,e] and schizandrin (**1**),[4g] in racemic form had appeared in the literature when we started this work. Although the asymmetric total syntheses of **1** and **3** have been reported by Meyers, his synthesis led to the production of the antipodes of the natural products.[4h]

In this paper, we present the total syntheses of (+)-schizandrin (**1**), (+)-gomisin A (**2**), and (+)-isoschizandrin (**3**) in their natural configurations, utilizing methodology which is widely applicable to the total synthesis of the other lignans from *Schisandra chinensis* in optically pure forms.[5]

Results and Discussion

Retrosynthetic Considerations. The outline of our total synthesis is illustrated in Scheme 1. The suitably

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(3) (a) Whiting, D. A. *Nat. Prod. Rep.* **1985**, *2*, 191. (b) Whiting, D. A. *Nat. Prod. Rep.* **1987**, *4*, 499. (c) MacRae, W. D.; Towers, G. H. N. *Phytochemistry* **1984**, *23*, 1207. (d) Ayres, D. C.; Loike, J. D. *Chemistry & Pharmacology of Natural Products: Lignans; Chemical, Biological and Clinical Properties*; Cambridge University Press: Cambridge, 1990.

(4) As to the leading synthetic studies of lignans from *Schisandra chinensis*, see follows. Deoxyschizandrin and wuweizisu C: (a) Kochetkov, N. K.; Khorlin, A.; Chizhov, O. S. *Tetrahedron Lett.* **1962**, 361. (b) Ghera, E.; David, Y. B.; Becker, D. *Tetrahedron Lett.* **1977**, 463. (c) Biftu, T.; Hazra, B. G.; Stevenson, R. *J. Chem. Soc. Perkin Trans. 1* **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. Since the publication of our preliminary reports, several total synthesis of related lignans were reported. See as follows: (i) Takeya, T.; Ohguchi, A.; Arai, Y.; Tobinaga, S. *Chem. Pharm. Bull.* **1994**, *42*, 430. (j) Takeya, T.; Ohguchi, A.; Tobinaga, S. *Chem. Pharm. Bull.* **1994**, *42*, 438. Gomisin N and γ-schizandrin: (k) Tanaka, M.; Ohshima, T.; Mitsuhashi, H.; Maruno, M.; Wakamatsu, T. *Heterocycles* **1994**, *37*, 739.

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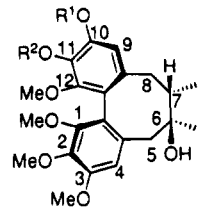
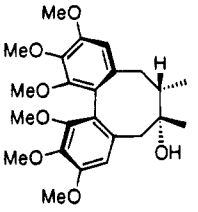


R^1=R^2=Me; (+)-schizandrin (1)
R^1,R^2=CH_2; (+)-gomisin A (2)



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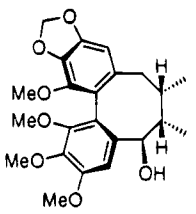
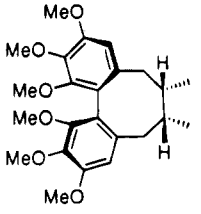
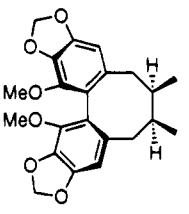


(-)-gomisin O (4)



(+)-deoxyschizandrin (5)



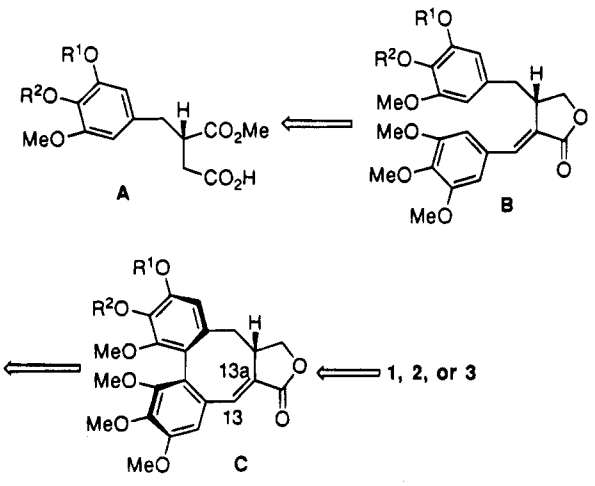
(-)-wuweizisu C (6)

substituted succinate **A** was selected as the starting material because optically pure **A** is available by several methods in both configurations. The transformation of **A** to the benzylidene lactone **B** followed by an oxidative coupling reaction would lead to the key tetracyclic intermediate **C** which possesses a dibenzocyclooctene nucleus with the intended biphenyl configuration. Although this strategy was first applied for the synthesis of dibenzocyclooctene lignans by Landais and co-workers in the total synthesis of racemic deoxyschizandrin,[4f] the most useful structural feature of compounds of type **C** was overlooked. The double bond at the C13–C13a position is ideally suited for the introduction of the C6 or C5 hydroxyl group of the natural lignans. In our syntheses, the introduction of the C6 tertiary hydroxyl group of **1**–**3** were planned by taking advantage of the C13–C13a double bond of compound **C** using the proper transformation(s).

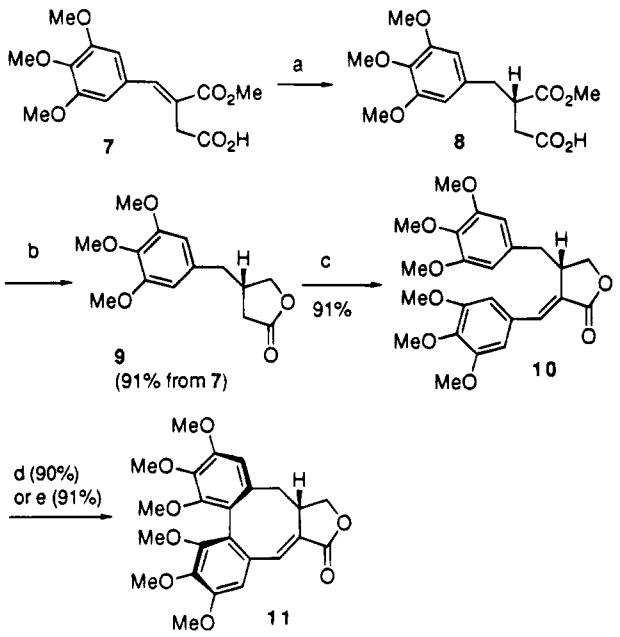
Total Synthesis of (+)-Schizandrin: 1. Preparation and Structural Confirmation of the Tetracyclic Key Intermediates.[5a,b] The synthesis of (+)-**1** started with the preparation of (−)-**11**, which corresponds to compound **C**, according to the sequence reported by Landais et al.[4f] from optically active **8**.[6] The mild and efficient Rh$^-$-(*R*,*R*)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis[bis(4-methoxy-3,5-dimethylphenyl)phosphino]-butane (MOD-DIOP)-catalyzed asymmetric hydrogenation[7] of the itaconic acid derivative **7**[4f] proceeded highly enantioselectively, and optically active (*S*)-**8** (>94% ee) was obtained quantitatively. The conversion of **8** to lactone **9**[4f] followed by enantio enrichment by recrystallization afforded optically active (−)-**9** with an $[\alpha]_D^{25}$ of −8.5° (*c* 1.13, $CHCl_3$) in 91% yield from **7** (the reported optical rotation for the antipode of **9** was +6.6° (*c* 0.76, $CHCl_3$)).[6] An aldol condensation–dehydration then provided *E*-benzylidene lactone (+)-**10** as the sole product (Scheme 2).

Before proceeding with the synthesis, the oxidative coupling reaction of (±)-**10** to (±)-**11** was examined with the reported tetrakis(trifluoroacetoxy)ruthenium mediated conditions[4f,8] and afforded the product in 91% yield. Because of the significance of the stereostructure of **11**, exhaustive structural confirmation had to be carried out.[9] The 2-D NOESY spectrum of (±)-**11** in $CDCl_3$ showed cross peaks between the hydrogens indicated by curve arrows in Chart 1 suggesting that **11** possesses the desired relative configuration between the biphenyl moiety and C3a position. Furthermore, the coupling constants between the hydrogens at C3, C3a, and C4 (Table 1) were consistent with dihedral angles determined by inspection of the Dreiding model ($\phi_{3\alpha-3a}$ = 160° ($J_{3\alpha-3a}$ = 10.2 Hz), $\phi_{3\beta-3a}$ = 40° ($J_{3\beta-3a}$ = 8.9 Hz), $\phi_{4\alpha-3a}$ = 70° ($J_{4\alpha-3a}$ = 1.5 Hz), and $\phi_{4\beta-3a}$ = 50° ($J_{4\beta-3a}$ = 6.8 Hz)).

Scheme 1



Scheme 2[a]



[a] (a) H_2, $Rh(COD)_2BF_4$, (*R*,*R*)-MOD-DIOP, Et_3N, MeOH, rt; (b) $NaBH_4$, $CaCl_2$, KOH, EtOH, 0 °C; HCl, rt; (c) LDA, 3,4,5-trimethoxybenzaldehyde, THF, −70 °C; Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt; DBU, toluene, 70 °C; (d) $Fe(ClO_4)_3$·$6H_2O$, CF_3CO_2H–CH_2Cl_2 (1:10), rt; (e) $Ru(OCOCF_3)_4$, CF_3CO_2H, BF_3·OEt_2, CH_2Cl_2, rt.

(6) The optical resolution of **8** with ephedrine has been reported. However, the overall recovery of the optically pure material was low. Brown, E.; Robin, J. P.; Dhal, R. *Tetrahedron* **1982**, *38*, 2569.

(7) Morimoto, T.; Chiba, M.; Achiwa, K. *Tetrahedron Lett.* **1989**, *30*, 735.

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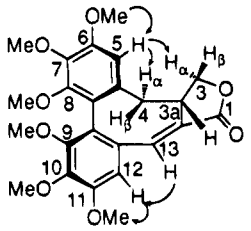
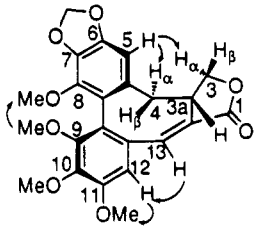
(9) The comparison of the reported physical data for (±)-**11** and those of the compound in our hand did not show a complete match. See ref 4f.

Chart 1. Observation of the Cross Peaks in the NOESY Spectrum of the Oxidative Coupling Products (11, 33, 34)



11



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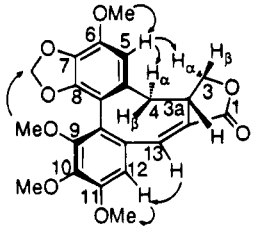

34

Finally, a single crystalline X-ray diffraction analysis confirmed the structure of (±)-**11**.[26]

Although oxidative coupling with $Ru(OCOCF_3)_4$ was successful, the cost of this reagent and its failure in converting **32** to **33** (see below) made us search for other conditions. Treatment of (±)-**10** with various oxidizing agents[11b,12-15] (except for the highly toxic vanadium[4c,d,10] or thallium[11] salts) was examined, and iron(III) chloride,[11b,13] manganese(III) acetylacetonate,[14] cobalt(III) fluoride,[11b] or iron(III) perchlorate[12] in trifluoroacetic acid were found to provide (±)-**11** (Table 2). Among these results, the efficient transformation with iron(III) perchlorate is noteworthy, because this cheap and trivial reagent has not been reported to effect the oxidative coupling reaction.[4i-k,5,12] Eventually, the oxidative coupling reaction of (+)-**10** was carried out reproducibly using iron(III) perchlorate as the oxidizing agent in trifluoroacetic acid and dichloromethane (1:10),[5a] affording the desired key intermediate (−)-**11** in comparable yield (90%) to that using $Ru(OCOCF_3)_4$.[16]

2. Introduction of the Tertiary Hydroxyl Group.[5b] The introduction of the tertiary hydroxyl group at the C6 position was the next task for the transformation of (−)-**11** to (+)-**1**. At first, the routes through the readily available compounds (**12** or **13**) were examined taking advantage of the double bond at the C6 position (Scheme 3).

After the quantitative reduction of (±)-**11** with diisobutylaluminum hydride (DIBAH), allylic alcohol (±)-**13** was acetylated to (±)-**14**. The palladium catalyzed Tsuji reduction of (±)-**14**[17] followed by alkaline hydrolysis afforded exo-methylene compound (±)-**12** in high yield without contamination by endo-olefinic compound **16**. Dihydroxylation of (±)-**12** with osmium tetraoxide provided the desired triols ((±)-**17** and (±)-**18**) albeit with low stereoselectivity (4:1).[18] The triol mixture was mesylated and treated with sodium hydride to afford the easily separable epoxy-methanesulfonates ((±)-**19** and (±)-**20**) in a ratio of 4:1. The reduction of major stereoisomer (±)-**19** with lithium aluminum hydride ($LiAlH_4$) completed the synthesis of (±)-(**1**). The spectroscopic data (^{1}H-NMR, IR, and MS) for the synthetic material were identical to those of the natural (+)-**1**,[2b] demonstrating the success of the total synthesis.

To avoid the low stereoselectivity of the dihydroxylation step of (±)-**12** (4:1) as well as tedious lengthy steps (eight steps from (±)-**11**), more stereoselective and concise routes were examined (Scheme 4). (−)-**13** was stereoselectively epoxidized with *tert*-butyl hydroperoxide in the presence of vanadyl acetylacetonate giving a single epoxide (+)-**21** quantitatively. After fruitless attempts using catalytic hydrogenolysis or metal hydride reductions, the cleavage of the C5−O bond of (+)-**21** was achieved with sodium in liquid ammonia giving methanesulfonate (+)-**22** in 45% yield, after the mesylation. Then, $LiAlH_4$ reduction of (+)-**22** in refluxing tetrahydrofuran (88%) finished the synthesis of (+)-**1**. Although the synthesis was completed in fewer steps as intended (four steps from (−)-**11**), the low yield of the oxirane

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(11) (a) Schwartz, M. A.; Wallace, R. A. *Tetrahedron Lett.* **1979**, 3257. (b) Mckillop, A.; Turrell, A. G.; Young, D. W.; Taylor, E. C. *J. Am. Chem. Soc.* **1980**, *102*, 6504. (c) Taylor, E. C.; Andrade, J. G.; Rall, G. J. H.; Mckillop, A. *J. Am. Chem. Soc.* **1980**, *102*, 6513. (d) Nishiyama, S.; Yamamura, S. *Chem. Lett.* **1981**, 1511. (e) Magnus, P.; Schultz, J.; Gallagher, T. *J. Am. Chem. Soc.* **1985**, *107*, 4984. (f) Taafrout, M.; Landais, Y.; Robin, J. P. *Tetrahedron Lett.* **1986**, *27*, 1781.

(12) $Fe(ClO_4)_3$ derived complexes were known to effect the oxidative coupling reaction, but $Fe(ClO_4)_3$ itself in CF_3CO_2H has not been utilized for the purpose of the biphenyl synthesis. Murase, M.; Kotani, E.; Okazaki, K.; Tobinaga, S. *Chem. Pharm. Bull.* **1986**, *34*, 3159.

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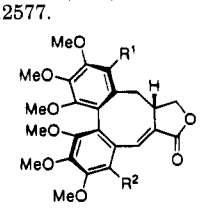
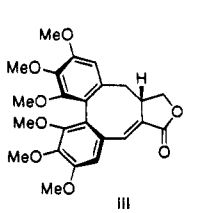
(15) The examples of the oxidative coupling reactions utilizing the organic oxidative reagents, see: (a) White, J. D.; Butlin, R. J.; Hahn, H. G.; Johnson, A. T. *J. Am. Chem. Soc.* **1990**, *112*, 8595. (b) Pelter, A.; Ward, R. S.; Jones, D. M.; Maddocks, P. *Tetrahedron Asymm.* **1992**, *3*, 239.

(16) The careful inspection of the reaction mixture showed the formation of the small amount of chlorinated products (**i** and **ii**) in 0.3% and 0.4% yield, respectively. However, the formation of the diastereomer of **11** (**iii**) could not be detected. The physical data for **i** and **ii** are as follows. (±)-**i**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.92 (dd, J = 6, 14.5 Hz, 1H), 3.19 (dd, J = 2, 14.5 Hz, 1H), 3.54−3.59 (m, 1H), 3.54 (s, 3H), 3.64 (s, 3H), 3.899 (s, 3H), 3.903 (s, 3H), 3.93 (s, 3H), 3.96 (s, 3H), 4.19 (dd, J = 9, 10 Hz, 1H), 4.45 (t, J = 9 Hz, 1H), 6.60 (s, 1H), 7.55 (d, J = 3.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.84, 41.25, 56.01, 60.74, 60.78, 60.94, 61.14, 61.16, 68.80, 106.32, 121.30, 122.08, 128.12, 129.95, 130.26, 130.29, 136.37, 142.39, 145.95, 149.86, 151.03, 151.89, 153.77, 171.39; MS m/z 476 (M^+, 100), 478 (M^+ + 2, 37); HRMS m/z for $C_{24}H_{25}ClO_8$ (M^+) 476.12380, found 476.12492. (±)-**ii**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.45 (dd, J = 1.5, 14 Hz, 1H), 2.99 (d, J = 7, 14 Hz, 1H), 3.51−3.57 (m, 1H), 3.60 (s, 3H), 3.63 (s, 3H), 3.87 (s, 3H), 3.89 (s, 3H), 3.96 (s, 3H), 4.00 (s, 3H), 4.09 (dd, J = 8, 10 Hz, 1H), 4.49 (t, J = 8 Hz, 1H), 6.41 (s, 1H), 7.49 (d, J = 3.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.68, 39.27, 56.12, 60.64, 60.90, 60.90, 61.19, 61.21, 68.11, 108.0, 122.14, 123.18, 126.07, 129.42, 130.31, 130.93, 134.90, 142.20, 147.39, 150.07, 150.91, 151.94, 153.32, 170.77; MS m/z 476 (M^+, 100), 478 (M^+ + 2, 37); HRMS m/z for $C_{24}H_{25}ClO_8$ (M^+) 476.12380, found 476.12577.



I: R^1=Cl, R^2=H
II: R^1=H, R^2=Cl



III

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(18) The epoxidation of (±)-**16** with MCPBA afforded **20** (R = H) and **19** (R = H) in 78% yield with reverse stereoselectivity (6:1). See ref 5c.

Table 1. ^{1}H-NMR Data of the Oxidative Coupling Products ((±)-11, (−)-33, (−)-34) in $CDCl_3$ at 500.13 MHz

	11	33	34
C3-H(α)	4.10 (dd, J = 8.4, 10.2 Hz)	4.09 (dd, J = 9, 10 Hz)	4.12 (dd, J = 10, 8 Hz)
C3-H(β)	4.47 (ddd, J = 0.5, 8.4, 8.9 Hz)	4.47 (t, J = 9 Hz)	4.47 (t, J = 8 Hz)
C3a-H	3.49−3.54 (m)	3.40−3.60 (m)	3.45−3.62 (m)
C4-H(α)	2.46 (dd, J = 1.5, 14.1 Hz)	2.43 (dd, J = 1.2, 14.2 Hz)	2.45 (dd, J = 1.4, 14.2 Hz)
C4-H(β)	3.06 (dd, J = 6.8, 14.1 Hz)	2.99 (dd, J = 6.6, 14.2 Hz)	3.07 (dd, J = 6.7, 14.2 Hz)
C5-H	6.41 (s)	6.34 (s)	6.28 (s)
-OMe	3.59 (s), 3.64 (s), 3.87 (s), 3.89 (s), 3.90 (s), 3.91 (s)	3.64 (s), 3.81 (s), 3.90 (s), 3.92 (s)	3.71 (s), 3.89 (s), 3.91 (s), 3.94 (s)
-OCH_2O-		5.96 (d, J = 1.5 Hz)	5.88 (d, J = 1.5 Hz)
		5.98 (d, J = 1.5 Hz)	5.89 (d, J = 1.5 Hz)
C12-H	6.59 (d, J = 0.5 Hz)	6.58 (s)	6.61 (s)
C13-H	7.53 (dt, J = 3.5, 0.5 Hz)	7.51 (d, J = 3 Hz)	7.51 (dt, J = 3.5, 0.5 Hz)

Table 2. Oxidative Coupling Reactions of (±)-10 to (±)-11[a]

condition	time (h)	yield of 11 (%)[b]
$Ru(OCOCF_3)_4$, CF_3CO_2H−CH_2Cl_2−BF_3·OEt_2	26	91[c]
$FeCl_3$, CF_3CO_2H	25	35 (85)[d,e]
$Mn(acac)_3$, CF_3CO_2H	4.5	63[f]
CoF_3, CF_3CO_2H	28	81[g]
$Fe(ClO_4)$·$6H_2O$, CF_3CO_2H	2.5	89[h]
$Fe(ClO_4)$·$6H_2O$, CF_3CO_2H−CH_2Cl_2[i]	1	91

[a] All reactions were carried out at room temperature. [b] Isolated yield. [c] See ref 8. [d] Yield in the parenthesis is that based on the consumed **10**. [e] See ref 13. [f] See ref 14. [g] See ref 11b. [h] See reference 12. [i] CF_3CO_2H−CH_2Cl_2 (1:10).

cleavage step was disappointing. Therefore, the introduction of the hydroxyl group to **13** was attempted using osmium tetraoxide. Dihydroxylation of (−)-**13** with osmium tetraoxide in pyridine, followed by mesylation of the resultant tetraol and $LiAlH_4$ reduction resulted in the synthesis of (+)-**1** in only three steps. However, this synthesis turned out to give the worst overall yield (29% from (−)-**13**).

To avoid the difficulty of cleaving the C5−O bond associated with epoxidation or dihydroxylation reactions, we then examined the hydration reaction of olefinic compounds reported by Mukaiyama (Scheme 5).[19] The cobalt(II) acetylacetonate-catalyzed hydration[19a−d] of diacetate (−)-**14** proceeded as expected, but the product was a 1:1 mixture of two diastereomers (**24** and **25**). The structures of these products were determined by converting them into the methanesulfonates ((+)-**22** or (+)-**26**), which were then correlated to (+)-**1** and (+)-**3**, respectively. On the other hand, the manganese(II) acetylacetonate-catalyzed hydration[19e] of the tetracyclic lactone (−)-**11** proceeded with a more satisfactory stereoselectivity affording the desired hydroxy lactone (−)-**27** as the major product in 70% yield, together with minor diastereomer (+)-**28** (11%).

The usefulness of this hydration reaction was emphasized by the straightforward three step conversion of hydroxy lactone (−)-**27** to schizandrin (**1**). Successive treatments of (−)-**27** with $LiAlH_4$, methanesulfonyl chloride, and $LiAlH_4$ afforded (+)-**1** in 63% overall yield from (−)-**27**. The physical properties ($[\alpha]_D$, ^{1}H-NMR, IR, MS, and mp) unambiguously established the identity of synthetic and natural schizandrins, including absolute configuration. Similarly, the minor hydroxy lactone (+)-**28** was transformed into (+)-**3**[2c] by way of (+)-**26**, confirming the structure of (+)-**28** and (+)-**26**.

Total Synthesis of (+)-Gomisin A.[5b] The optically pure succinate (−)-**29**, as the starting material for the total synthesis of (+)-**2**, was obtained by Achiwa's asymmetric hydrogenation of **30** or the optical resolution of racemic **29** (Scheme 6). The asymmetric hydrogenation of itaconic acid derivative **30**[20] afforded **29** in quantitative yield, and the enantio excess of >94% was determined by HPLC analysis of its morpholine amide (chiralcell OC, Daicel). Since the solubility of (±)-**29** in methanol was considerably lower than that of optically pure **29**, enantio enrichment to 100% ee was easily achieved by extraction with a small amount of methanol (84% yield from **30**).

This simple enantio enrichment procedure made the optical resolution method the most practical option for the preparation of optically pure **29**. After extensive screening of various chiral amines, the resolution of (±)-**29** was attained by using *D*-α-amino-ε-caprolactam giving (−)-**29** with 66% ee and a yield of 61%. Extraction with methanol then gave (−)-**29** with high optical purity (>98% ee) in 41% recovery (27% overall recovery from (±)-**29**).

The optically pure (−)-**29** was then converted into *E*-benzylidene lactone (+)-**32** through (−)-**31**. The preparation of key intermediate (−)-**33** was not straightforward in this instance. The oxidative coupling reaction of (+)-**32** with iron(III) perchlorate provided two regioisomeric products (−)-**33** (46%) and (−)-**34** (7%) (Scheme 7). The similarity of the coupling patterns of the hydrogens at the C3, C3a, and C4 positions in the ^{1}H NMR spectra of each product compared with those of **11** suggested that both products possessed the desired configuration (Table 1). By the inspection of NOESY spectra, the cross peak between the C5-H and the methoxy group was observed only for the minor product suggesting an ortho relationship between the C5-H and the methoxy group. Consequently, it was concluded that the minor product was regioisomer (−)-**34**, and hence, the major product was the desired one ((−)-**33**).

While the reaction of (+)-**32** with various oxidizing reagents including $Ru(OCOCF_3)_4$ did not improve the regioselectively or yield,[21] it was found that the oxidative coupling of (+)-**35**, obtained by the demethylenation of (+)-**32**,[22] proceeded regioselectively affording only the desired isomer **36** in good yield. Cyclooctene **36** was then methylenated to (−)-**33** in 62% overall yield from (+)-**35**.

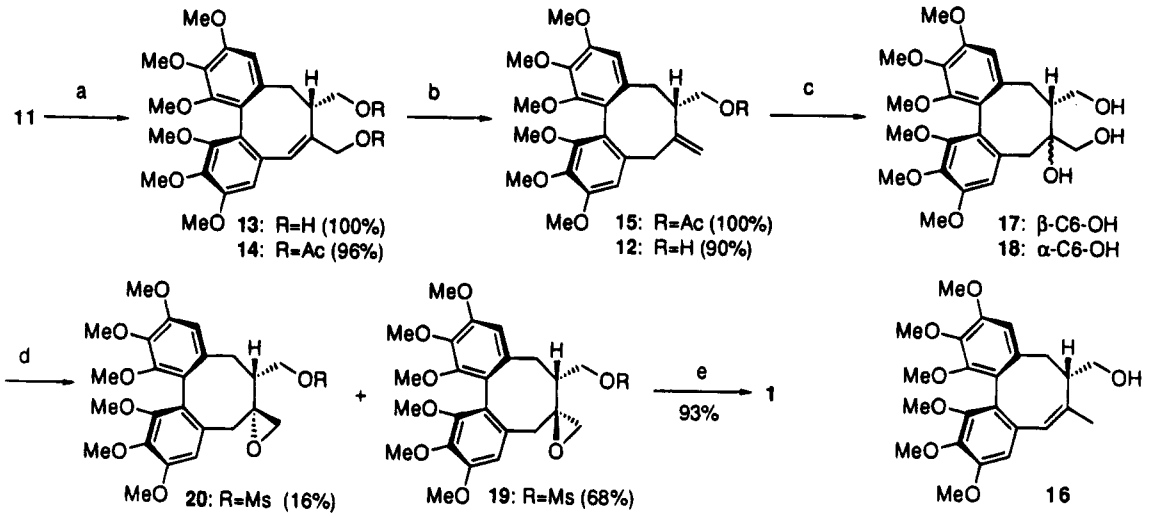
(19) (a) Mukaiyama, T.; Isayama, S.; Inoki, S.; Kato, K.; Yamada, T.; Takai, T. *Chem. Lett.* **1989**, 449. (b) Inoki, S.; Kato, K.; Takai, T.; Isayama, S.; Yamada, T.; Mukaiyama, T. *Chem. Lett.* **1989**, 515. (c) Isayama, S.; Mukaiyama, T. *Chem. Lett.* **1989**, 569. (d) Isayama, S.; Mukaiyama, T. *Chem. Lett.* **1989**, 1071. (e) Inoki, S.; Kato, K.; Isayama, S.; Mukaiyama, T. *Chem. Lett.* **1991**, 1869.

(20) Schneider, G. E.; Stevenson, R. *J. Chem. Soc., Perkin Trans 1* **1982**, 999.

(21) The oxidative coupling of (±)-**31** with tetrakis(trifluoroacetoxy)-ruthenium afforded (±)-**33** in only 12% yield. The unsuccessful coupling reaction owing to the oxidative demethylenation was also reported by Robin. See ref 4f.

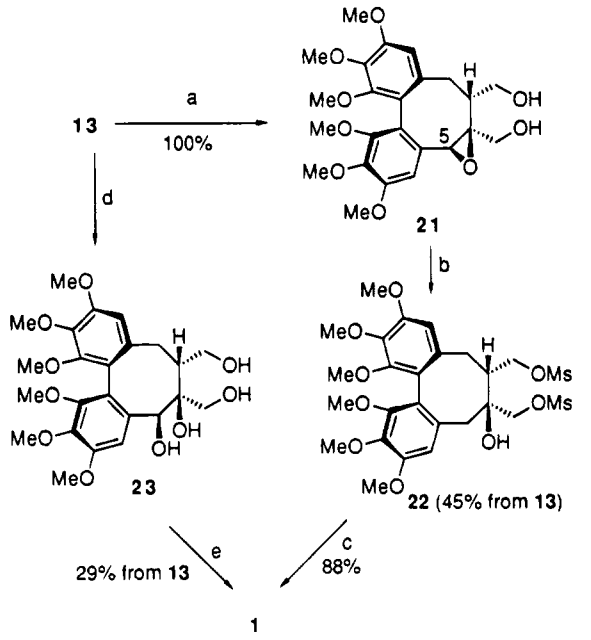
(22) Gerecke, M.; Borer, R.; Brossi, A. *Helv. Chim. Acta* **1976**, *59*, 2551.

Scheme 3[a]



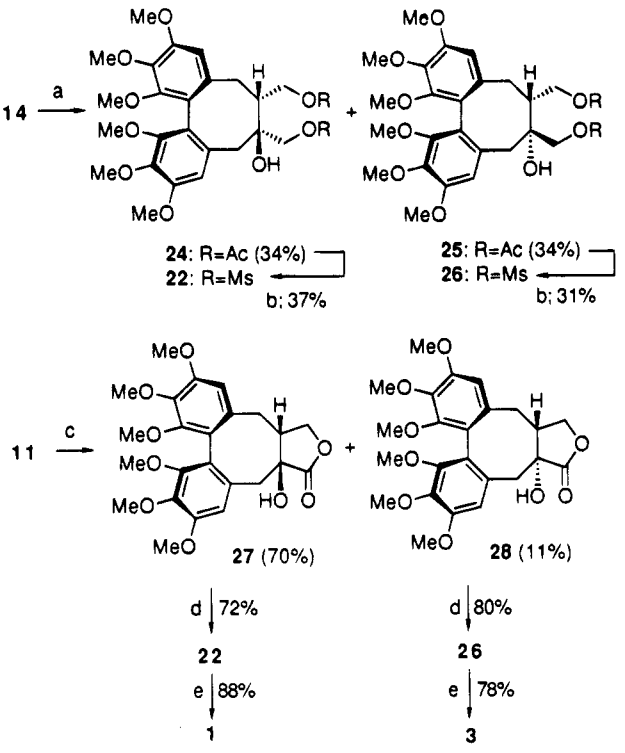
[a] (a) DIBAH, THF, 0 °C; Ac_2O, pyridine, rt; (b) $Pd(PPh_3)_2Cl_2$, HCO_2NH_4, THF, reflux; NaOH, MeOH, rt; (c) OsO_4, pyridine, rt; (d) MsCl, pyridine, 0 °C; NaH, THF, 0 °C; (e) $LiAlH_4$, THF, reflux.

Scheme 4[a]



[a] (a) *t*-BuOOH, $VO(acac)_2$, CH_2Cl_2, reflux; (b) Na, liquid NH_3, THF, −78 °C; MsCl, pyridine, 0 °C; (c) $LiAlH_4$, THF, reflux; (d) OsO_4, pyridine, rt; (e) MsCl, pyridine, 0 °C; $LiAlH_4$, THF, reflux.

Scheme 5[a]

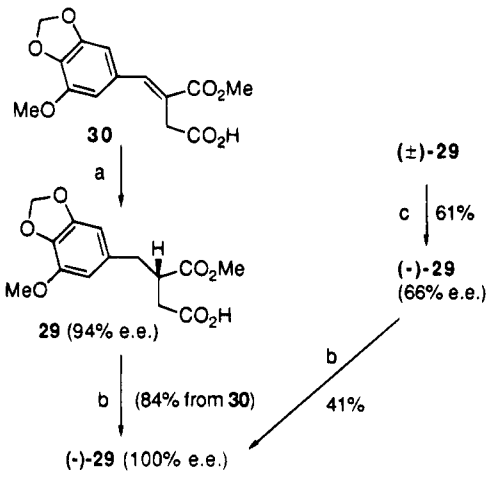


[a] (a) O_2, $Co(acac)_2$, $PhSiH_3$, THF, rt; (b) K_2CO_3, MeOH, rt; MsCl, pyridine, 0 °C; (c) O_2, $Mn(acac)_2$, $PhSiH_3$, 2-PrOH, rt; (d) $LiAlH_4$, THF, reflux; MsCl, pyridine, 0 °C; (e) $LiAlH_4$, THF, reflux.

The synthetic attempts to (+)-**2** from (−)-**33** through the exo-methylene compound (+)-**41** or the epoxide (+)-**38** were disappointing due to the low stereoselectivity of the dihydroxylation step or the undesired reductive methylenedioxy ring cleavage of **38** (Scheme 8). A successful synthesis was achieved by Mukaiyama's hydration reaction (Scheme 9). The hydration of (−)-**33** with manganese(II) acetylacetonate as a catalyst afforded (−)-**44** as the major isomer (67%). Successive reduction ($LiAlH_4$), mesylation and reduction ($LiAlH_4$) provided (+)-**2** in good yield. The physical properties of the synthetic gomisin A were in accord with those of the natural product.[2b]

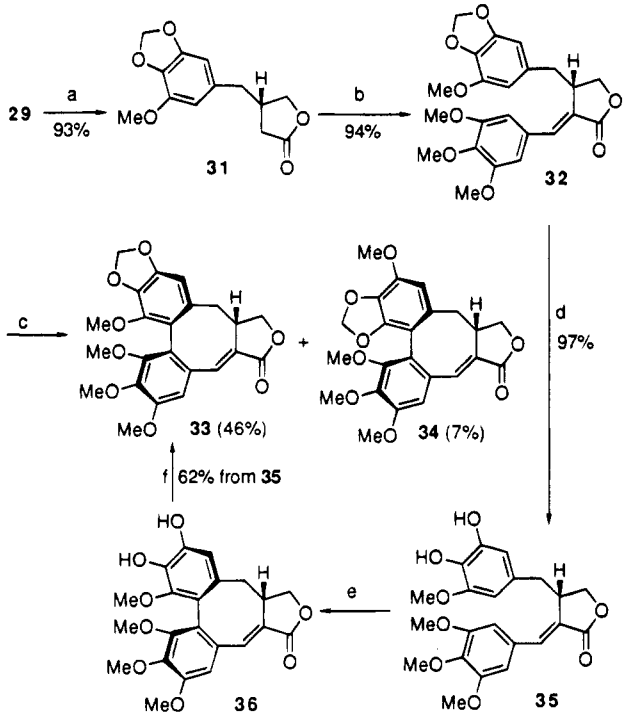
Total Synthesis of (+)-Isoschizandrin.[5c] For the synthesis of (+)-isoschizandrin (**3**), a tertiary hydroxyl group must be introduced at the C6 position with the opposite stereochemistry as (+)-**1** or (+)-**2**. Since none of the methods described above offered a stereoselective way to create the C6 stereocenter with an *R*-configuration, the introduction of the C6 hydroxyl had to be achieved by a new method. Inspection of molecular models indicated that the β-benzylic hydrogen in compound (**D**) is below the plane of the C6 double bond (Scheme 10). Furthermore, conformational analysis of **48** using molecular mechanics calculations supported this observation, suggesting that in the most stable conformation, the C5 hydroxyl exists below the plane of the C6 double bond.[23] This finding led us to believe that a hydroxyl-directed epoxidation would result in the formation of the stereochemically desired product **52** if the

Scheme 6[a]



[a] (a) H_2, $Rh(COD)_2BF_4$, (*R,R*)-MOD-DIOP, Et_3N, MeOH, rt; (b) MeOH extraction; (c) D-α-amino-ε-caprolactam, acetone; oxalic acid.

Scheme 7[a]



[a] (a) $NaBH_4$, $CaCl_2$, KOH, EtOH, 0 °C; HCl, rt; (b) LDA, 3,4,5-trimethoxybenzaldehyde, THF, −70 °C; Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt; DBU, toluene, 80 °C; (c) $Fe(ClO_4)_3{\cdot}6H_2O$, CF_3CO_2H–CH_2Cl_2 (1:10), rt; (d) BCl_3, CH_2Cl_2, 0 °C; HCl, MeOH, rt; (e) $Fe(ClO_4)_3{\cdot}6H_2O$, CF_3CO_2H–CH_2Cl_2 (1:1), rt; (f) CH_2Br_2, K_2CO_3, DMF, 60 °C.

conformation of **48** at the transition state was similar to that of the ground state.[24]

On the basis of this analysis, the synthesis of (+)-**3** was undertaken. The key intermediate (+)-**48** was prepared from (−)-**13** by way of epoxydiol (+)-**21**. After successive epoxidation and methanesulfonylation of (−)-**13**, the resultant epoxymesylate (+)-**49** was treated with sodium iodide in refluxing methyl isobutyl ketone affording a mixture of diiodide **50** and iodide **51**. Zinc treatment of the mixture caused the reduction of the iodomethyl group to a methyl group as well as reductive opening of the epoxy-iodide moiety of **50** to provide (+)-**48**.

Vanadyl acetylacetonate catalyzed epoxidation of (+)-**48** with *tert*-butyl hydroperoxide afforded **52**, which was directly methanesulfonylated to give (+)-**53** as a single diastereomer (92% from **48**). The stereostructure of (+)-**53** was unambiguously confirmed by completing the synthesis. Cleavage of the methanesulfonyloxyl group and oxirane ring by sodium borohydride reduction in DMF provided (+)-**3** as a crystalline solid.[25] A careful examination of the crude reaction product by ^{1}H-NMR spectroscopy showed no sign of contamination by (+)-**1** (the diastereomer of (+)-**3** at the C6 position), suggesting the high stereoselectivity of the epoxidation step. The spectroscopic data (^{1}H-NMR, IR, and MS) and optical rotation of the synthetic material were identical to those of natural isoschizandrin.[2c]

In summary, the total syntheses of (+)-schizandrin, (+)-gomisin A, and (+)-isoschizandrin with natural configuration were achieved for the first time. In these syntheses, the newly developed oxidative coupling reaction was effectively utilized for the preparation of the key intermediates. Furthermore, in the case of schizandrin and gomisin A, the introduction of a C6 hydroxyl group was achieved in a very concise manner by means of the Mukaiyama hydration reaction. In the case of isoschizandrin, the C6 hydroxyl group was introduced with opposite streochemistry by taking advantage of the conformation of (+)-**48**.

Experimental Section

(*S*)-(*E*)-3-(3,4,5-Trimethoxybenzyl)butanolide ((−)-9). A solution of $Rh(COD)_2BF_4$ (550 mg, 1.34 mmol) and (*R,R*)-MOD-DIOP (1.12 g, 1.55 mmol) in freshly distilled MeOH (500 mL) was stirred under argon at room temperature for 10 min and then added to a solution of **7** (257 g, 0.83 mol) and Et_3N (115 mL, 0.80 mol) in freshly distilled MeOH (1 L). The mixture was stirred at room temperature under a hydrogen atmosphere for 42 h. A 0.5 N aqueous NaOH solution was added, and the mixture was extracted with CH_2Cl_2. The aqueous layer was acidified with 6 N HCl and extracted with CH_2Cl_2, and the combined extracts were dried over $MgSO_4$. After evaporation of the solvent, **8** was obtained as a pale yellow oil (250 g). A mixture of **8** (250 g), KOH (85%, 52.5 g, 0.80 mmol), $CaCl_2$ (100 g, 0.90 mmol), and $NaBH_4$ (68 g, 1.8 mol) in EtOH (2.7 L) was stirred at 0 °C for 12 h. After addition of 6 N HCl, the mixture was extracted with CH_2Cl_2, and the combined extracts were dried over $MgSO_4$. Evaporation of the solvent afforded a colorless solid, which was recrystallized from AcOEt to give (−)-**9** as colorless prisms (201 g, 91% from **7**): mp 101.5–103 °C; IR (KBr, cm^{-1}) 2992, 2972, 2928, 1766, 1592; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.31 (dd, J = 7, 17 Hz, 1H), 2.63 (dd, J = 8, 17 Hz, 1H), 2.71 (d, J = 9 Hz, 2H), 2.79–2.94 (m, 1H), 3.84 (s, 3H), 3.85 (s, 6H), 4.06 (dd, J = 6, 9 Hz, 1H), 4.36 (dd, 7, 9 Hz, 1H), 6.36 (s, 2H); MS *m/z* 266 (M^+), 181 (100); $[\alpha]^{25}_D$ −8.50° (*c* 1.13, $CHCl_3$). Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81. Found: C, 63.02; H, 6.87.

(*S*)-(*E*)-3-(3,4,5-Trimethoxybenzyl)-2-(3,4,5-trimethoxybenzylidene)butanolide ((+)-10). To a solution containing diisopropylamine (6.5 mL, 46 mmol) in THF (40 mL) under

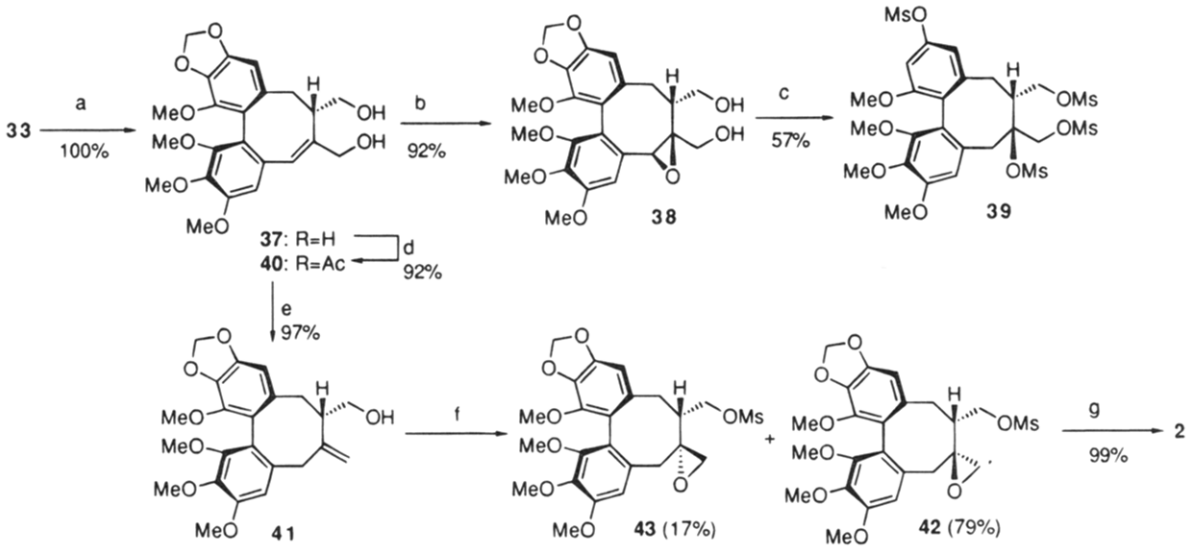
(23) Molecular mechanics calculations were carried out with the CHARMm/QUANTA (version 3.32, Polygen Corporation) software package implemented on graphics workstation IRIS 4D/220 (Silicon Graphics).

(24) As to the discussion on the structure of the transition state of the V(+5)-TBHP epoxidations, see: Sharpless, K. B.; Verhoeven, T. R. *Aldrichim. Acta* **1979**, *12*, 63.

(25) (+)-Isoschizandrin was isolated as crystalline solid for the first time.

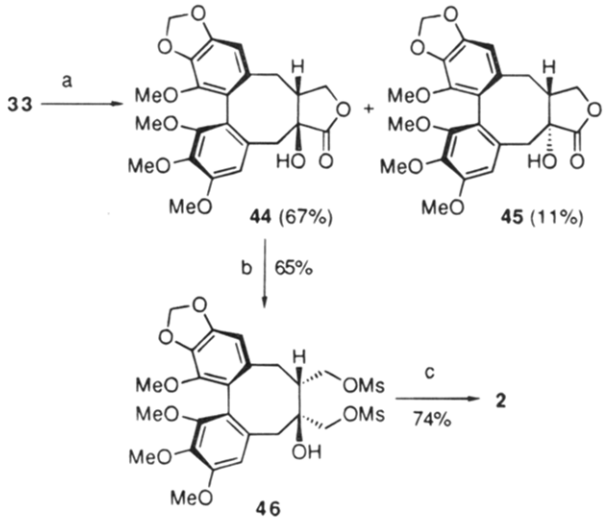
(26) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

Scheme 8[a]



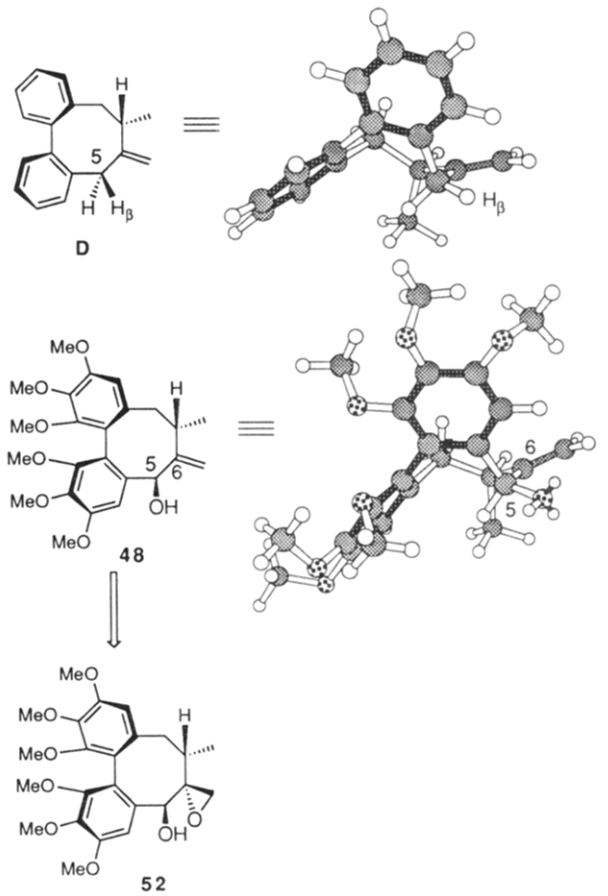
[a] (a) DIBAH, THF, 0 °C; (b) *t*-BuOOH, $VO(acac)_2$, CH_2Cl_2, reflux; (c) Li, liquid NH_3, THF, *t*-BuOH, −78 °C; MsCl, pyridine, 0 °C; (d) Ac_2O, pyridine, 0 °C; (e) $Pd(PPh_3)_2Cl_2$, HCO_2NH_4, THF, reflux; NaOH, MeOH, rt; (f) OsO_4, pyridine, rt; MsCl, pyridine, 0 °C; NaH, THF, 0 °C; (g) $LiAlH_4$, THF, reflux.

Scheme 9[a]



[a] (a) O_2, $Mn(acac)_2$, $PhSiH_3$, 2-PrOH, rt; (b) $LiAlH_4$, THF, reflux; MsCl, pyridine, 0 °C; (c) $LiAlH_4$, THF, reflux.

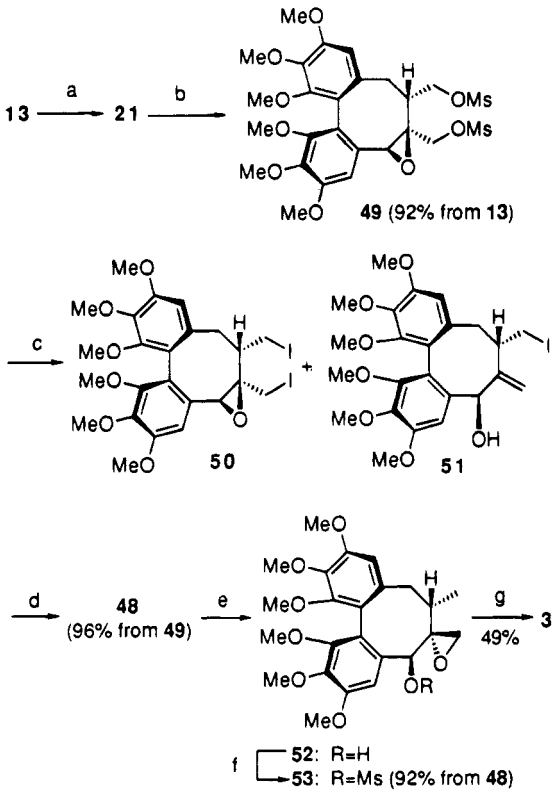
Scheme 10



argon at −70 °C was added *n*-butyllithium (1.6 M in hexane, 28 mL, 45 mmol). Stirring at −70 °C was continued for 10 min, followed by the addition of (−)-**9** (10.0 g, 38 mmol) in THF (100 mL). The mixture was stirred at −70 °C for 30 min, followed by the addition of the 3,4,5-trimethoxybenzaldehyde (8.8 g, 45 mmol) in THF (20 mL). Stirring was continued for 5 min, followed by the addition of a saturated aqueous NH_4Cl solution. The mixture was extracted with AcOEt, the combined extracts were washed successively with 2 N HCl, H_2O, saturated $NaHCO_3$ solution, and brine and dried over $MgSO_4$. The residue obtained after the evaporation of the solvent was dissolved in CH_2Cl_2 (100 mL), then Et_3N (8.0 mL, 58 mmol), Ac_2O (5.0 mL, 53 mmol), and DMAP (200 mg, 1.6 mmol) were added, and the solution was stirred at room temperature for 1 h. The mixture was washed successively with 2 N 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 (100 mL), DBU (10 mL, 64.5 mmol) 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 2 N HCl, H_2O, saturated $NaHCO_3$ solution, and brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on a silica gel column (AcOEt−hexane = 2:3) to afford (+)-**10** (15.2 g, 91%) as a colorless solid: mp 88.5−90.0 °C (colorless needles from AcOEt−hexane); IR ($CHCl_3$, cm^{-1}) 2940, 1748, 1648, 1588; ^1H NMR (200 MHz, $CDCl_3$) δ 2.65 (dd, J = 10, 14 Hz, 1H), 3.11 (d, J = 5, 14 Hz, 1H), 3.82 (s, 3H), 3.83 (s, 6H), 3.89 (s, 6H), 3.91 (s, 3H), 3.82−3.91 (m, 1H), 4.29−4.31 (m, 2H), 6.38 (s, 2H), 6.82 (s, 2H), 7.53 (d, J = 2 Hz, 1H); MS *m/z* 444 (M^+), 181 (100); $[\alpha]^{24}_D$ +82.9° (*c* 0.92, $CHCl_3$). Anal. Calcd for $C_{24}H_{28}O_8$: C, 64.85; H, 6.35. Found: C, 64.71, H. 6.35.

Oxidative Coupling Reaction of (±)-10 to (3a*RS*,*SR*-Biar)-3a,4-dihydro-6,7,8,9,10,11-hexamethoxydibenzo-

Scheme 11[a]



[a] (a) *t*-BuOOH, $VO(acac)_2$, CH_2Cl_2, reflux; (b) MsCl, pyridine, 0 °C; (c) NaI, methyl isobutyl ketone, reflux; (d) Zn, AcOH, MeOH, rt; (e) *t*-BuOOH, $VO(acac)_2$, CH_2Cl_2, reflux; (f) MsCl, pyridine, 0 °C; (g) $NaBH_4$, DMF, 80 °C.

[4,5:6,7]cycloocta[1,2-*c*]furan-1(3*H*)-one ((±)-11). (a) Ru(OCOCF$_3$)$_4$–BF$_3$·OEt$_2$–CF$_3$CO$_2$H. According to the procedure reported by Landais *et al.*, (±)-**11** was prepared from (±)-**10** in 91%: mp 153–154.5 °C (colorless prisms from AcOEt–hexane); IR (KBr, cm^{-1}) 2936, 2836, 1758, 1674, 1594; ^1H NMR (see Table 1); MS *m/z* 442 (M^+, 100). Anal. Calcd for $C_{24}H_{26}O_8$: C, 65.15; H, 5.92. Found: C, 64.95; H, 5.70. Compound (±)-**11** crystallized from AcOEt in space group *P*1 (no. 1) with a = 11.994(2) Å, b = 12.770(1) Å, c = 8.141(3) Å, α = 100.79(1)°, β = 91.42(2)°, γ = 115.41(1)°, V = 1082.6(2) Å, z = 2, and d_{calcd} = 1.338 g/cm^3. The intensity data were measured on a Enraf Nonius CAD-4 System (Cu Kα (λ = 1.54184 Å) radiation). Of the 4472 reflection collected, 4004 were considered to be observed [$I > 3.00\sigma(I)$]. The structure was solved by direct method (MULTAN) and the final discrepancy indices were R = 0.054 and R_w = 0.046.

(b) Fe(ClO$_4$)$_3$–CF$_3$CO$_2$H. To a solution of (±)-**10** (3.0 g, 6.8 mmol) in CF_3CO_2H (20 mL) was added $Fe(ClO_4)_3 \cdot 6H_2O$ (9.37 g, 20.3 mmol), and the mixture was stirred at room temperature for 2.5 h. Workup as described above gave (±)-**11** as colorless prisms (2.66 g, 89%). The physical data were completely identical to those of previously obtained (±)-**11**.

(c) CoF$_3$–CF$_3$CO$_2$H. To a solution of (±)-**10** (106 mg, 0.24 mmol) in CF_3CO_2H (2 mL) was added CoF_3 (62 mg, 0.53 mmol), and the mixture was stirred at room temperature for 28 h. Workup as described above gave (±)-**11** as colorless prisms (86 mg, 81%). The physical data were completely identical to those of previously obtained (±)-**11**.

(d) FeCl$_3$–CF$_3$CO$_2$H. To a solution of (±)-**10** (90 mg, 0.20 mmol) in CF_3CO_2H (1 mL) was added $FeCl_3$ (65 mg, 0.40 mmol), and the mixture was stirred at room temperature for 25 h. Workup as described above gave (±)-**11** as colorless prisms (31 mg, 35%) and recovered (±)-**10** (53 mg, 59%). The physical data were completely identical to those of previously obtained (±)-**11**.

(e) Mn(acac)$_3$–CF$_3$CO$_2$H. To a solution of (±)-**10** (90 mg, 0.20 mmol) in CF_3CO_2H (1 mL) was added $Mn(acac)_3$ (210 mg, 0.60 mmol), and the mixture was stirred at room temperature for 4.5 h. Workup as described above gave (±)-**11** as colorless prisms (57 mg, 63%). The physical data were completely identical to those of previously obtained (±)-**11**.

(3a*S*,*R*-Biar)-3a,4-Dihydro-6,7,8,9,10,11-hexamethoxydibenzo[4,5:6,7]cycloocta[1,2-*c*]furan-1(3*H*)-one ((−)-11). A mixture of (+)-**10** (491 mg, 1.1 mmol), $Fe(ClO_4)_3 \cdot 6H_2O$ (1.47 g, 3.2 mmol), and CF_3CO_2H (0.44 mL) in CH_2Cl_2 (5 mL) was stirred at room temperature for 2 h. The mixture was washed successively with 6 N HCl, H_2O, and saturated $NaHCO_3$ solution and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on a silica gel column (AcOEt–hexane = 1:1) to give (−)-**11** as a pale yellow oil (441 mg, 90%): IR ($CHCl_3$, cm^{-1}) 2940, 1754, 1668, 1596; ^1H NMR (200 MHz, $CDCl_3$) δ 2.46 (d, J = 14 Hz, 1H), 3.07 (dd, J = 7, 14 Hz, 1H), 3.40–3.60 (m, 1H), 3.59 (s, 3H), 3.64 (s, 3H), 3.88 (s, 3H), 3.89 (s, 3H), 3.90 (s, 3H), 3.92 (s, 3H), 4.11 (dd, J = 8, 10 Hz, 1H), 4.47 (t, J = 8 Hz, 1H), 6.41 (s, 1H), 6.59 (s, 1H), 7.53 (d, J = 3 Hz, 1H); MS *m/z* 442 (M^+, 100); HRMS *m/z* for $C_{24}H_{26}O_8$ (M^+) 442.16277, found 442.16347; $[\alpha]^{26}_D$ −284° (*c* 0.895, $CHCl_3$).

(7*S*,*R*-Biar)-7,8-Dihydro-6,7-bis(hydroxymethyl)-1,2,3,10,11,12-hexamethoxydibenzo[*a*,*c*]cyclooctene ((−)-13). DIBAH (1.5 M in toluene, 2 mL, 3 mmol) was added to a solution of (+)-**11** (380 mg, 0.86 mmol) in THF (10 mL), and the mixture was stirred at 0 °C for 20 min. After addition of acetone (20 mL), the mixture was washed successively with 2 N HCl, H_2O, saturated $NaHCO_3$ solution, and brine and dried over $MgSO_4$. After evaporation of the solvent, (−)-**13** was obtained as a colorless solid (380 mg, 100%): mp 120.5–121.5 °C (colorless needles from AcOEt–hexane); IR ($CHCl_3$, cm^{-1}) 3424, 2940, 2844, 1594; ^1H NMR (200 MHz, $CDCl_3$) δ 1.90 (br, 1H), 2.51 (dd, J = 13, 18 Hz, 1H), 2.70 (br, 1H), 2.96–3.06 (m, 2H), 3.52 (s, 3H), 3.68 (s, 3H), 3.84 (s, 6H), 3.87 (s, 3H), 3.91 (s, 3H), 3.60–4.00 (m, 2H), 4.09 (d, J = 12 Hz, 1H), 4.16 (d, J = 12 Hz, 1H), 6.43 (s, 1H), 6.48 (s, 1H), 6.54 (s, 1H); MS *m/z* 446 (M^+), 428 (100); $[\alpha]^{24}_D$ −204.8° (*c* 0.31, $CHCl_3$). Anal. Calcd for $C_{24}H_{30}O_8$: C, 64.56; H, 6.77. Found: C, 64.29; H, 6.83.

(7*RS*,*SR*-Biar)-7,8-Dihydro-6,7-bis(hydroxymethyl)-1,2,3,10,11,12-hexamethoxydibenzo[*a*,*c*]cyclooctene ((±)-13). (±)-**11** (137.7 mg, 0.31 mmol) was reduced with DIBAH as described above affording (±)-**13** as colorless prisms (139 mg, 100%): mp 161.5–162.5 °C (from AcOEt–hexane); IR (KBr, cm^{-1}) 3524, 1488; ^1H NMR (200 MHz, $CDCl_3$) δ 1.57 (br, 2H), 2.51 (dd, J = 13, 18 Hz, 1H), 2.97–3.06 (m, 2H), 3.52 (s, 3H), 3.68 (s, 3H), 3.85 (s, 6H), 3.87 (s, 3H), 3.91 (s, 3H), 3.79–4.00 (m, 2H), 4.09 (d, J = 12 Hz, 1H), 4.16 (d, J = 12 Hz, 1H), 6.43 (s, 1H), 6.48 (s, 1H), 6.53 (s, 1H); MS *m/z* 446 (M^+, 100). Anal. Calcd for $C_{24}H_{30}O_8$: C, 64.56; H, 6.77. Found: C, 64.34; H, 6.87.

(7*RS*,*SR*-Biar)-6,7-Bis(acetoxymethyl)-7,8-dihydro-1,2,3,10,11,12-hexamethoxydibenzo[*a*,*c*]cyclooctene ((±)-14). A solution of (±)-**13** (600 mg, 1.35 mmol) and Ac_2O (4 mL) in pyridine (7 mL) was stirred at room temperature for 14 h, and the mixture was taken up into AcOEt. The mixture was washed successively with 6 N HCl, H_2O, saturated $NaHCO_3$ solution, and brine and dried over $MgSO_4$. After evaporation of the solvent, the residue was crystallized from Et_2O and hexane to give (±)-**14** as colorless needles (683 mg, 96%): mp 127–127.5 °C; IR (KBr, cm^{-1}) 2936, 1738, 1594, 1486; ^1H NMR (200 MHz, $CDCl_3$) δ 2.04 (s, 3H), 2.05 (s, 3H), 2.45 (dd, J = 12, 18 Hz, 1H), 3.00–3.13 (m, 2H), 3.52 (s, 3H), 3.66 (s, 3H), 3.85 (s, 6H), 3.88 (s, 3H), 3.91 (s, 3H), 4.16 (d, J = 7 Hz, 2H), 4.48 (d, J = 13 Hz, 1H), 4.54 (d, J = 13 Hz, 1H), 6.40 (s, 1H), 6.47 (s, 1H), 6.59 (s, 1H); MS *m/z* 530 (M^+, 100). Anal. Calcd for $C_{28}H_{34}O_{10}$: C, 63.38; H, 6.46. Found: C, 62.98; H, 6.36.

(7*RS*,*SR*-Biar)-7-(Acetoxymethyl)-5,6,7,8-tetrahydro-1,2,3,10,11,12-hexamethoxy-6-methylenedibenzo[*a*,*c*]cyclooctene ((±)-15). A mixture of (±)-**14** (643 mg, 1.21 mmol), HCO_2NH_4 (800 mg, 12.7 mmol), and $Pd(PPh_3)_2Cl_2$ (60 mg, 0.09 mmol) in THF (25 mL) was heated under reflux for 19 h. The reaction mixture was taken up into AcOEt, washed successively with saturated $NaHCO_3$ solution, and brine and dried over $MgSO_4$. After evaporation of the solvent, the residue was

chromatographed on a silica gel column (AcOEt–hexane = 1:2) to give (±)-**15** as a colorless solid (584 mg, 100%): mp 149.5–151 °C (colorless needles from AcOEt and hexane); IR (KBr, cm^{-1}) 2936, 1730, 1598, 1488; ^1H NMR (200 MHz, $CDCl_3$) δ 2.09 (s, 3H), 2.52 (d, J = 12 Hz, 1H), 2.75–2.84 (m, 2H), 2.93 (d, J = 12 Hz, 1H), 3.06 (d, J = 12 Hz, 1H), 3.61 (s, 3H), 3.63 (s, 3H), 3.865 (s, 3H), 3.869 (s, 3H), 3.892 (s, 3H), 3.897 (s, 3H), 3.96–4.15 (m, 2H), 4.81 (d, J = 2 Hz, 1H), 5.03 (d, J = 2 Hz, 1H), 6.64 (s, 1H), 6.58 (s, 1H); MS m/z 472 (M^+, 100). Anal. Calcd for $C_{26}H_{32}O_8$: C, 66.08; H, 6.83. Found: C, 66.00; H, 6.92.

(7*RS*,*SR*-Biar)-5,6,7,8-Tetrahydro-7-(hydroxymethyl)-1,2,3,10,11,12-hexamethoxy-6-methylenedibenzo[*a*,*c*]-cyclooctene ((±)-12). A solution of (±)-**15** (540 mg, 1.14 mmol) and 2 N aqueous NaOH solution (1 mL, 2 mmol) in MeOH (10 mL) and THF (10 mL) was stirred at room temperature for 20 min. 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, the residue was chromatographed on a silica gel column (AcOEt–hexane = 1:1) to give (±)-**12** as a colorless solid (441 mg, 90%): mp 143.5–145 °C (colorless prisms from AcOEt–hexane); IR (KBr, cm^{-1}) 3504, 2932, 1634, 1596, 1488; ^1H NMR (200 MHz, $CDCl_3$) δ 1.43 (d, J = 10 Hz, 1H), 2.51–2.69 (m, 2H), 2.78 (dd, J = 5, 13 Hz, 1H), 2.94 (d, J = 12 Hz, 1H), 3.05 (d, J = 12 Hz, 1H), 3.28 (t, J = 10 Hz, 1H), 3.60–3.82 (m, 1H), 3.61 (s, 3H), 3.63 (s, 3H), 3.87 (s, 3H), 3.89 (s, 6H), 3.90 (s, 3H), 4.83 (d, J = 2 Hz, 1H), 5.13 (br, 1H), 6.63 (s, 1H), 6.66 (s, 1H); MS m/z 430 (M^+, 100). Anal. Calcd for $C_{24}H_{30}O_7$: C, 66.96; H, 7.02. Found: C, 66.81; H, 7.00.

(6*RS*,7*SR*,*SR*-Biar)-Spiro[5,6,7,8-tetrahydro-7-[(methanesulfonyloxy)methyl]-1,2,3,10,11,12-hexamethoxydibenzo[*a*,*c*]cyclooctene-6,2′-oxirane] ((±)-19) and (6*RS*,7*RS*,*RS*-Biar)-Spiro[5,6,7,8-tetrahydro-7-[(methanesulfonyloxy)methyl]-1,2,3,10,11,12-hexamethoxydibenzo[*a*,*c*]-cyclooctene-6,2′-oxirane] ((±)-20). A solution of (±)-**12** (209 mg, 0.49 mmol) and OsO_4 (177 mg, 0.696 mmol) in pyridine (2.5 mL) was stirred at room temperature for 4.5 h. After addition of saturated aqueous $NaHSO_3$ solution, the mixture was stirred at room temperature for 17 h and extracted with AcOEt. The combined extracts were washed successively with 2 N HCl, H_2O, saturated $NaHCO_3$ solution, and brine and dried over $MgSO_4$. After evaporation of the solvent, the crude mixture of (±)-**17** and (±)-**18** was dissolved in pyridine (1 mL), methanesulfonyl chloride (0.25 mL) was added, and the mixture was stirred at 0 °C for 1 h and taken up into AcOEt. The mixture was washed successively with H_2O, 2 N HCl, H_2O, saturated $NaHCO_3$ solution, and brine and dried over $MgSO_4$. After evaporation of the solvent, the residue was dissolved in THF (10 mL), NaH (60% in mineral oil, 30 mg, 0.75 mmol) was added, and the mixture was stirred 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, the residue was chromatographed on a silica gel column (AcOEt–hexane = 1:1) to give (±)-**20** as a colorless solid (41 mg, 16%) and (±)-**19** as a colorless oil (173 mg, 68%). (±)-**20**: mp 117–118 °C (colorless needles from AcOEt–hexane); IR ($CHCl_3$, cm^{-1}) 2936, 1596, 1360, 1328; ^1H NMR (200 MHz, $CDCl_3$) δ 1.72–1.90 (m, 1H), 2.03 (d, J = 13 Hz, 1H), 2.60–2.69 (m, 2H), 2.88–3.02 (m, 3H), 3.04 (s, 3H), 3.61 (s, 6H), 3.88 (s, 3H), 3.89 (s, 3H), 3.90 (s, 3H), 3.95 (s, 3H), 4.23–4.33 (m, 2H), 6.45 (s, 1H), 6.81 (s, 1H); MS m/z 524 (M^+, 100); HRMS m/z for $C_{25}H_{32}SO_{10}$ (M^+) 524.17162, found 524.17013. (±)-**19**: IR ($CHCl_3$, cm^{-1}) 2940, 1598, 1362, 1342; ^1H NMR (200 MHz, $CDCl_3$) δ 1.70–1.84 (m, 1H), 2.19 (d, J = 14 Hz, 1H), 2.75 (d, J = 14 Hz, 1H), 2.84 (d, J = 5 Hz, 1H), 2.92 (d, J = 5 Hz, 1H), 2.79–2.86 (m, 2H), 3.03 (s, 3H), 3.61 (s, 3H), 3.64 (s, 3H), 3.88 (s, 3H), 3.90 (s, 3H), 3.91 (s, 3H), 3.92 (s, 3H), 4.08 (dd, J = 7, 10 Hz, 1H), 4.29 (dd, J = 8, 10 Hz, 1H), 6.50 (s, 1H), 6.66 (s, 1H); MS m/z 524 (M^+), 428 (100); HRMS m/z for $C_{25}H_{32}SO_{10}$ (M^+) 524.17162, found 524.17333.

Synthesis of (±)-Schizandrin (1). To a refluxing solution of $LiAlH_4$ (350 mg, 9.2 mmol) in THF (5 mL) was added a solution of (±)-**19** (317 mg, 0.60 mmol) in THF (5 mL), and the resultant mixture was heated under reflux for 15 min. The reaction was quenched with $Na_2SO_4{\cdot}10H_2O$ and stirred at room temperature for 1 h, and the insoluble material was filtered off. After evaporation of the solvent, the residue was chromatographed on a silica gel column (AcOEt–hexane = 1:2) to give (±)-schizandrin (**1**) as a colorless solid (242 mg, 93%): mp 126–127 °C (colorless prisms from Et_2O–hexane); IR ($CHCl_3$, cm^{-1}) 3572, 2936, 2840, 1596; ^1H NMR (200 MHz, $CDCl_3$) δ 0.82 (d, J = 7 Hz, 3H), 1.26 (s, 3H), 1.75–1.93 (m, 2H), 2.30–2.44 (m, 2H), 2.56–2.70 (m, 2H), 3.58 (s, 3H), 3.59 (s, 3H), 3.88 (s, 3H), 3.884 (s, 3H), 3.89 (s, 3H), 3.892 (s, 3H), 6.54 (s, 1H), 6.61 (s, 1H); MS m/z 432 (M^+, 100). These data were identical to those of natural schizandrin.

(5*S*,6*S*,7*R*,*R*-Biar)-5,6-Epoxy-5,6,7,8-tetrahydro-6,7-bis(hydroxymethyl)-1,2,3,10,11,12-hexamethoxydibenzo[*a*,*c*]-cyclooctene ((+)-21). A solution of (−)-**13** (647 mg, 1.45 mmol), $VO(acac)_2$ (10 mg, 0.038 mmol), and t-BuOOH (3.0 M in 2,2,4-trimethylpentane, 1.0 mL, 3.0 mmol) in CH_2Cl_2 (20 mL) was stirred at room temperature for 15 min, and then 10% aqueous $FeSO_4$ solution was added. After stirring at room temperature for 2 h, the organic layer was separated, washed with H_2O, and dried over $MgSO_4$. After evaporation of the solvent, (+)-**21** was obtained as pale yellow oil (702 mg, 100%). This material was used in the next reaction without further purification: IR ($CHCl_3$, cm^{-1}) 3456, 3000, 2936, 2840, 1596, 1574, 1486; ^1H NMR (200 MHz, $CDCl_3$) δ 1.40–1.64 (m, 1H), 2.28–2.44 (m, 1H), 2.66 (dd, J = 9, 15 Hz, 1H), 2.84 (dd, J = 10, 15 Hz, 1H), 3.06–3.22 (m, 2H), 3.62 (s, 1H), 3.65 (s, 3H), 3.68 (s, 3H), 3.70–3.92 (m, 3H), 3.88 (s, 3H), 3.89 (3H, s), 3.906 (s, 3H), 3.91 (s, 3H), 6.59 (s, 1H), 6.72 (s, 1H); MS m/z 462 (M^+, 100); HRMS m/z for $C_{24}H_{30}O_9$ (M^+) 462.18898, found 462.18857; $[\alpha]^{27}_D$ +15.4° (c 0.475, $CHCl_3$).

(6*S*,7*R*,*R*-Biar)-5,6,7,8-Tetrahydro-6-hydroxy-6,7-bis[(methanesulfonyloxy)methyl]-1,2,3,10,11,12-hexamethoxydibenzo[*a*,*c*]cyclooctene ((+)-22). Na (50 mg) was added to a liquid NH_3 (15 mL) at −78 °C followed by the addition of (+)-**21** (100 mg, 0.22 mmol) in THF (2 mL), the resultant mixture was stirred at −78 °C for 10 min, and saturated NH_4Cl was added. After evaporation of NH_3, the residue was taken up into AcOEt, washed successively with H_2O and brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was dissolved in pyridine (1 mL), methanesulfonyl chloride (0.4 mL) was added, and the mixture was stirred at room temperature for 1.5 h. AcOEt was added, the mixture was washed successively with 2 N HCl, H_2O, and saturated $NaHCO_3$ solution, and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on a silica gel column (AcOEt–hexane = 2:1) to give (+)-**22** as a colorless amorphous solid (60 mg, 45% from **13**): IR ($CHCl_3$, cm^{-1}) 3560, 2940, 1596, 1460, 1402, 1360, 1170, 1128, 1106; ^1H NMR (200 MHz, $CDCl_3$) δ 1.80 (br, 1H), 2.30–2.50 (m, 1H), 2.41 (d, J = 14 Hz, 1H), 2.58 (d, J = 14 Hz, 1H), 2.70–2.80 (m, 2H), 3.07 (s, 3H), 3.17 (s, 3H), 3.63 (s, 3H), 3.65 (s, 3H), 3.92 (s, 3H), 3.94 (s, 3H), 3.95 (s, 3H), 3.96 (s, 3H), 4.10–4.25 (m, 4H), 6.55 (s, 1H), 6.78 (s, 1H); MS m/z 620 (M^+), 428 (100); HRMS m/z for $C_{26}H_{36}S_2O_{13}$ (M^+) 620.15974, found 620.16277; $[\alpha]^{27}_D$ +73.0° (c 0.24, $CHCl_3$).

Synthesis of (+)-Schizandrin from (+)-22. To a refluxing solution of $LiAlH_4$ (1.0 g, 26 mmol) in THF (30 mL) was added a solution of (+)-**22** (2.24 g, 3.61 mmol) in THF (30 mL), and the resultant mixture was heated under reflux for 15 min. The reaction was quenched with $Na_2SO_4{\cdot}10H_2O$, stirred at room temperature for 1 h, and the insoluble material was filtered off. After evaporation of the solvent, the residue was chromatographed on a silica gel column (AcOEt–hexane = 1:2) to give (+)-schizandrin (**1**) as a colorless solid (1.38 g, 88%): mp 131–132 °C; IR (KBr, cm^{-1}) 3524, 2960, 2932, 1596; ^1H NMR (200 MHz, $CDCl_3$) δ 0.83 (d, J = 7 Hz, 3H), 1.26 (s, 3H), 1.80–1.96 (m, 2H), 2.37 (d, J = 13 Hz, 1H), 2.38 (dd, J = 14, 7 Hz, 1H), 2.66 (dd, J = 14, 2 Hz, 1H), 2.67 (d, J = 13 Hz, 1H), 3.58 (s, 3H), 3.60 (s, 3H), 3.88 (s, 3H), 3.89 (s, 3H), 3.89 (s, 3H), 3.91 (s, 3H), 6.54 (s, 1H), 6.61 (s, 1H); MS m/z 432 (M^+), 414 (100); HRMS m/z for $C_{24}H_{32}O_7$ (M^+) 432.21480, found 432.21508; $[\alpha]^{25}_D$ +88.0° (c 0.775, $CHCl_3$). These data were identical to those of natural schizandrin.

Synthesis of (+)-Schizandrin from (−)-13 by Way of 23. A solution of (−)-**13** (102 mg, 0.23 mmol) and OsO_4 (62

mg, 0.24 mmol) in pyridine (2 mL) was stirred at room temperature for 30 min, and saturated $NaHSO_3$ solution was added. After stirring at room temperature for 45 min, AcOEt was added, and the mixture was washed successively with H_2O, 6 N HCl, saturated $NaHCO_3$ solution, and brine and dried over $MgSO_4$. To the residue obtained by the evaporation of the solvent were added pyridine (1 mL) and methanesulfonyl chloride (0.05 mL), and the mixture was stirred at room temperature for 5 h. AcOEt was added, and the mixture was washed successively with 2 N HCl, H_2O, saturated $NaHCO_3$ solution, and brine and dried over $MgSO_4$. By the evaporation of the solvent, crude methanesulfonate was obtained as a pale yellow oil (99.5 mg). A solution of crude methanesulfonate (28 mg) in THF (1 mL) was added to a refluxing solution of $LiAlH_4$ in THF (0.25 M, 2 mL, 0.5 mmol), and the mixture was heated under reflux for 30 min. AcOEt was added, the mixture was washed successively with 2 N HCl, H_2O, saturated $NaHCO_3$ solution, and brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography on a silica gel column (AcOEt–hexane = 1:3) to give (+)-schizandrin (**1**) as a colorless solid (8 mg, 29%). The physical data were completely identical to those of previously obtained (+)-**1**.

(7*S*,*R*-Biar)-6,7-Bis(acetoxymethyl)-7,8-dihydro-1,2,3,10,11,12-hexamethoxydibenzo[*a*,*c*]cyclooctene (−)-14. A solution of (−)-**13** (886 mg, 1.99 mmol) and Ac_2O (2 mL) in pyridine (5 mL) was stirred at room temperature for 3 h. The reaction mixture was taken up into AcOEt, washed successively with 2 N HCl, H_2O, saturated $NaHCO_3$ solution, and brine and then dried over $MgSO_4$. The evaporation of the solvent and recrystallization of the residue from AcOEt and hexane afforded (−)-**14** as colorless prisms (0.87 g, 83%): mp 125.5–127 °C; IR (KBr, cm^{-1}) 2936, 2836, 1740, 1730, 1594, 1574, 1486, 1464; ^1H NMR (200 MHz, $CDCl_3$) δ 2.36–2.52 (m, 1H), 3.00–3.15 (m, 2H), 2.04 (s, 3H), 2.05 (s, 3H), 3.52 (s, 3H), 3.66 (s, 3H), 3.85 (s, 6H), 3.88 (s, 3H), 3.92 (s, 3H), 4.16 (d, J = 7 Hz, 2H), 4.48 (d, J = 13 Hz, 1H), 4.84 (d, J = 13 Hz, 1H), 6.41 (s, 1H), 6.48 (s, 1H), 6.59 (s, 1H); MS m/z 530 (M^+, 100); $[\alpha]^{25}_D$ −123.6° (c 0.78, $CHCl_3$). Anal. Calcd for $C_{28}H_{34}O_{10}$: C, 63.38; H, 6.46. Found: C, 63.17; H, 6.49.

(6*S*,7*R*,*R*-Biar)-6,7-Bis(acetoxymethyl)-5,6,7,8-tetrahydro-6-hydroxy-1,2,3,10,11,12-hexamethoxydibenzo[*a*,*c*]cyclooctene (24) and (6*R*,7*R*,*R*-Biar)-6,7-bis(acetoxymethyl)-5,6,7,8-tetrahydro-6-hydroxy-1,2,3,10,11,12-hexamethoxydibenzo[*a*,*c*]cyclooctene (25) (Hydration of (−)-14). A mixture of (−)-**14** (100 mg, 0.19 mmol), $Co(acac)_2$ (10 mg, 0.039 mmol), and $PhSiH_3$ (0.1 mL, 0.81 mmol) in THF (5 mL) was stirred at 60 °C for 20 h under an oxygen atmosphere. After evaporation of the solvent, the residue was chromatographed on a silica gel column (Et_2O) to give **24** (36 mg, 35%) as a colorless oil and **25** (32 mg, 32%) as a colorless oil. These products were fully characterized by converting crude materials to (+)-**22** and (+)-**26** (see below). **24**: ^1H NMR (200 MHz, $CDCl_3$) δ 1.50–2.00 (br, 1H), 1.99 (s, 3H), 2.15 (s, 3H), 2.16–2.30 (m, 1H), 2.44 (d, J = 15 Hz, 1H), 2.60–2.73 (m, 3H), 3.60 (s, 3H), 3.61 (s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 3.91 (s, 6H), 4.10 (s, 2H), 4.12–4.25 (m, 2H), 6.55 (s, 1H), 6.63 (s, 1H). **25**: ^1H NMR ($CDCl_3$) δ 1.70–2.00 (br, 1H), 2.08 (s, 3H), 2.16 (s, 3H), 2.19–2.30 (m, 1H), 2.46 (dd, J = 8, 15 Hz, 1H), 2.58 (d, J = 15 Hz, 1H), 2.74 (dd, J = 15, 8 Hz, 1H), 2.88 (d, J = 15 Hz, 1H), 3.569 (s, 3H), 3.573 (s, 3H), 3.87 (s, 3H), 3.88 (s, 9H), 4.00–4.18 (m, 3H), 4.49 (dd, J = 9, 6 Hz, 1H), 6.64 (s, 2H).

Conversion of 24 to (+)-22. A mixture of crude **24** (36 mg) and K_2CO_3 (1 mg) in MeOH (2 mL) was stirred at room temperature for 1 h. After evaporation of the solvent, the residue was taken up into pyridine (0.5 mL), methanesulfonyl chloride (0.1 mL) was added, and the mixture was stirred at room temperature for 3 h. The mixture was taken up into AcOEt, washed successively with 2 N HCl, H_2O, and saturated $NaHCO_3$ solution, and then dried over $MgSO_4$. Concentration and chromatography on a silica gel column (AcOEt–hexane = 2:1) afforded (+)-**22** as a colorless amorphous solid (15 mg, 37%). The physical data were completely identical to those of previously obtained (+)-**22**.

(6*R*,7*R*,*R*-Biar)-5,6,7,8-Tetrahydro-6-hydroxy-6,7-bis[(methanesulfonyloxy)methyl]-1,2,3,10,11,12-hexamethoxydibenzo[*a*,*c*]cyclooctene (Conversion of 25 to (+)-26). Crude **25** (34 mg) was treated as described above to afford (+)-**26** as a colorless amorphous solid (12 mg, 31%): IR ($CHCl_3$, cm^{-1}) 3576, 3004, 2940, 2836, 1596, 1492, 1462, 1358, 1194, 1106; ^1H NMR (200 MHz, $CDCl_3$) δ 1.74 (br, 1H), 2.10–2.64 (m, 3H), 2.80–2.93 (m, 2H), 3.03 (s, 3H), 3.11 (s, 3H), 3.58 (s, 6H), 3.89 (s, 3H), 3.91 (s, 3H), 3.93 (s, 3H), 3.88 (s, 3H), 4.15–4.31 (m, 2H), 4.28 (d, J = 11 Hz, 1H), 4.60 (dd, J = 4, 10 Hz, 1H), 6.67 (s, 1H), 6.77 (s, 1H); MS m/z 620 (M^+), 524 (100); HRMS m/z for $C_{26}H_{36}S_2O_{13}$ (M^+) 620.15974, found 620.15931; $[\alpha]^{25}_D$ +108.96° (c 0.53, $CHCl_3$).

(3a*R*,13a*S*,*R*-Biar)-3a,4,13,13a-Tetrahydro-13a-hydroxy-6,7,8,9,10,11-hexamethoxydibenzo[4,5:6,7]cycloocta[1,2-*c*]furan-1(3*H*)-one ((−)-27) and (3a*R*,13a*R*,*R*-Biar)-3a,4,13,13a-tetrahydro-13a-hydroxy-6,7,8,9,10,11-hexamethoxydibenzo[4,5:6,7]cycloocta[1,2-*c*]furan-1(3*H*)-one ((+)-28). A mixture of (−)-**11** (1.0 g, 2.26 mmol), $Mn(acac)_2$ (670 mg, 2.32 mmol), and $PhSiH_3$ (2.0 mL, 16.2 mmol) in 2-PrOH (50 mL) was stirred under an oxygen atmosphere at room temperature for 24 h. After the addition of saturated $Na_2S_2O_3$ solution, solvent was evaporated off, and the residue was taken up into AcOEt, washed with H_2O, and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on a silica gel column (AcOEt–hexane = 2:3) to give (−)-**27** as a colorless solid (733 mg, 70%) and (+)-**28** as a colorless oil (111 mg, 11%): (−)-**27**: mp 178–179 °C (colorless needles from AcOEt–hexane); IR (KBr, cm^{-1}) 3476, 2940, 2832, 1760, 1596, 1402, 1128, 1110; ^1H NMR (200 MHz, $CDCl_3$) δ 2.68 (m, 6H), 3.637 (s, 3H), 3.643 (s, 3H), 3.88 (s, 3H), 3.89 (s, 3H), 3.90 (s, 3H), 3.92 (s, 3H), 3.85–3.95 (m, 1H), 4.40 (dd, J = 8, 9 Hz, 1H), 6.37 (s, 1H), 6.72 (s, 1H); MS m/z 460 (M^+, 100); $[\alpha]^{26}_D$ −13.6° (c 0.425, $CHCl_3$). Anal. Calcd for $C_{24}H_{28}O_9$: C, 62.60; H, 6.13. Found: C, 62.49; H, 6.15. (+)-**28**: IR ($CHCl_3$, cm^{-1}) 3580, 3004, 2940, 2840, 1778, 1598, 1574, 1486, 1462, 1432, 1126, 1106, 1002; ^1H NMR (200 MHz, $CDCl_3$) δ 1.78–1.94 (br, 1H), 2.10–2.30 (m, 1H), 2.57 (d, J = 13 Hz, 1H), 3.44 (d, J = 13 Hz, 1H), 2.73 (dd, J = 12, 15 Hz, 1H), 3.01 (dd, J = 7, 15 Hz, 1H), 3.57 (s, 3H), 3.72 (s, 3H), 3.84 (s, 3H), 3.88 (s, 3H), 3.89 (s, 6H), 4.05 (dd, J = 8, 10 Hz, 1H), 4.19 (t, J = 8 Hz, 1H), 6.41 (s, 1H), 6.55 (s, 1H); MS m/z 460 (M^+, 100); HRMS m/z for $C_{24}H_{28}O_9$ (M^+) 460.17333, found 460.17291; $[\alpha]^{26}_D$ +109.6° (c 0.585, $CHCl_3$).

(6*S*,7*R*,*R*-Biar)-5,6,7,8-Tetrahydro-6-hydroxy-6,7-bis[(methanesulfonyloxy)methyl]-1,2,3,10,11,12-hexamethoxydibenzo[*a*,*c*]cyclooctene ((+)-22 from (−)-27). To a refluxing solution of $LiAlH_4$ (1.0 g, 26 mmol) in THF (30 mL) was added a solution of (−)-**27** (2.32 g, 5.43 mmol) in THF (20 mL), and the resultant mixture was heated under reflux for 30 min. The reaction was quenched with $Na_2SO_4{\cdot}10H_2O$, stirred at room temperature for 1 h, and the insoluble material was filtered off. After evaporation of the solvent, the residue was dissolved in pyridine (10 mL), methanesulfonyl chloride (2.0 mL) was added, and the resultant mixture was stirred at 0 °C for 1.5 h. AcOEt was added, and the mixture was washed successively with 2 N HCl, H_2O, saturated $NaHCO_3$ solution, and brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on a silica gel column (AcOEt–hexane = 2:1) to give (+)-**22** as a colorless amorphous solid (2.24 g, 72%). The physical data were completely identical to those of previously obtained (+)-**22**.

(+)-26 from (+)-28. To a refluxing solution of $LiAlH_4$ (300 mg, 7.9 mmol) in THF (10 mL) was added a solution of (−)-**27** (365 mg, 0.79 mmol) in THF (10 mL), and the resultant mixture was heated under reflux for 20 min and cooled to room temperature. The reaction was quenched with $Na_2SO_4{\cdot}10H_2O$ and stirred at room temperature for 1 h, and the insoluble material was filtered off. After evaporation of the solvent, the residue was dissolved in pyridine (5 mL), methanesulfonyl chloride (0.3 mL) was added, and the resultant mixture was stirred at 0 °C for 1 h. AcOEt was added, and the mixture was washed successively with 2 N HCl, H_2O, saturated $NaHCO_3$ solution, and brine and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on a silica gel column (AcOEt–hexane = 2:1) to give (+)-**26**

as a colorless amorphous solid (394 mg, 80%). The physical data were completely identical to those of previously obtained (+)-**26**.

(+)-Isoschizandrin (3) from (+)-26. To a refluxing solution of $LiAlH_4$ (300 mg, 7.9 mmol) in THF (10 mL) was added a solution of (+)-**26** (300 mg, 0.4 mmol) in THF (5 mL), and the resultant mixture was heated under reflux for 30 min. The reaction was quenched with $Na_2SO_4 \cdot 10H_2O$ and stirred at room temperature for 1 h, and the insoluble material was filtered off. After evaporation of the solvent, the residue was chromatographed on a silica gel column (AcOEt−hexane = 1:2) to give (+)-isoschizandrin (**3**) as a colorless solid (164 mg, 78%). The physical data were identical in all respects to those of alternatively synthesized (+)-**3** (see below).

Asymmetric Hydrogenation of 30 and Enantio Enrichment of (−)-29. $Rh(COD)_2BF_4$ (230 mg, 0.57 mmol) and (*R,R*)-MOD-DIOP (458 mg, 0.63 mmol) was dissolved in freshly distilled MeOH (50 mL) and stirred under argon at room temperature for 10 min. The mixture was added to a solution of **30** (85.6 g, 0.29 mol) and freshly distilled Et_3N (40 mL, 0.29 mol) in freshly distilled MeOH (450 mL), and the resultant mixture was stirred at room temperature under a hydrogen atmosphere for 45 h. After addition of aqueous 0.5 N NaOH solution, the mixture was extracted with CH_2Cl_2. The aqueous layer was made acidic with 6 N HCl and extracted with CH_2Cl_2, and the combined extracts were dried over $MgSO_4$. The evaporation of the solvent gave (−)-**29** as a colorless solid (87.1 g, >94% ee), which was taken up into MeOH (200 mL) and stirred at room temperature for 4 h. After removal of the precipitate by filtration, the filtrate was concentrated to dryness to give (−)-**29** as a solid (53.8 g, >99% ee). The precipitate (37.7 g) was taken up into MeOH (70 mL) and stirred at room temperature for 12 h. The filtration and concentration of the filtrate gave additional (−)-**29** as a colorless solid (19.0 g, >99% ee; total amount 72.8 g, 84% from **30**): mp 96.5−97.0 °C (colorless prisms); IR (KBr, cm^{-1}) 3136, 2912, 1724, 1680, 1638; ^1H NMR (200 MHz, $CDCl_3$) δ 2.46 (dd, J = 4.5, 17 Hz, 1H), 2.62−2.77 (m, 2H), 2.93−3.13 (m, 2H), 3.69 (s, 3H), 3.88 (s, 3H), 5.94 (s, 2H), 6.31 (s, 1H), 6.34 (s, 1H); MS *m/z* 296 (M^+), 165 (100); $[\alpha]^{23}_D$ −26.6° (*c* 1.18, $CHCl_3$). Anal. Calcd for $C_{14}H_{16}O_7$: C, 56.75; H, 5.44. Found: C, 56.89; H, 5.29.

Determination of the Optical Purity of 29. A solution of **29** (60 mg), morpholine (0.017 mL), DCC (41 mg), and DMAP (10 mg) in CH_2Cl_2 (1 mL) was left stand at room temperature for 2 h. After evaporation of the solvent, the residue was taken up into AcOEt (2 mL) and supernatant was concentrated. The residue was dissolved in a mixture of 2-PrOH and hexane (1:1, 0.5 mL) and analyzed by HPLC with the following conditions (eluent; 2-PrOH-hexane 1:2 at 1.35 mL/min, stationary phase; diacel chiralcell OC, 5 mm Φ × 25 cm, UV detection at 250 nm).

Optical Resolution of (±)-29. A mixture of (±)-**29** (20 g, 67.6 mmol) and *D*-(+)-α-amino-ε-caprolactam (8.65 g, 67.6 mmol) in acetone (240 mL) was stirred at room temperature for 3 h, and the precipitated crystalline solid (17.54 g, 61.2%) was collected. The collected solid (17.54 g) was dissolved in saturated $NaHCO_3$ solution, washed with Et_2O, acidified with 10% aqueous oxalic acid solution, and extracted with CH_2Cl_2. The combined extracts were dried over $MgSO_4$ and concentrated to give (−)-**29** (12.29 g, 66% ee), which was taken up into MeOH (20 mL), and the mixture was stirred at room temperature for 1 h. The insoluble material was removed, and the filtrate was concentrated to give (−)-**29** (5.04 g, 41.0%) of >98% ee. The physical data were completely identical to those of previously obtained (−)-**29**.

(*S*)-(*E*)-3-[5-Methoxy-3,4-(methylenedioxy)benzyl]-butanolide ((−)-31). A mixture of (−)-**29** (19.04 g, 64.3 mmol), KOH (85%, 4.5 g, 68.3 mmol), $CaCl_2$ (13.7 g, 123.4 mol), and $NaBH_4$ (9.6 g, 252 mmol) in EtOH (350 mL) was stirred at 0 °C for 19 h, concentrated HCl (500 mL) was added, and the mixture was stirred at room temperature for 30 min and extracted with CH_2Cl_2. The combined extracts were washed successively with saturated $NaHCO_3$ solution and brine and dried over $MgSO_4$. Evaporation of the solvent and recrystallization of the residue from AcOEt and hexane gave (−)-**31** as colorless prisms (14.94 g, 93%): mp 88.5−89.5 °C; IR (KBr, cm^{-1}) 1784, 1768, 1632; ^1H NMR (200 MHz, $CDCl_3$) δ 2.27 (dd, J = 7, 17 Hz, 1H), 2.55−2.89 (m, 4H), 3.90 (s, 3H), 4.03 (dd, J = 6, 9 Hz, 1H), 4.34 (dd, J = 7, 9 Hz, 1H), 5.95 (s, 2H), 6.30 (d, J = 2 Hz, 1H), 6.34 (d, J = 2 Hz, 1H); MS *m/z* 250 (M^+), 165 (100); $[\alpha]^{23}_D$ −6.82° (*c* 1.12, $CHCl_3$). Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.38; H, 5.69.

(*S*)-(*E*)-3-[5-Methoxy-3,4-(methylenedioxy)benzyl]-2-(3,4,5-trimethoxybenzylidene)butanolide ((+)-32). To a solution containing diisopropylamine (3.5 mL, 24 mmol) in THF (20 mL) under argon at −70 °C was added *n*-butyllithium (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 (−)-**31** (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 aqueous NH_4Cl solution. The mixture was extracted with AcOEt, and the combined extracts were washed successively with 2 N 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), then Et_3N (7 mL), Ac_2O (5 mL), and DMAP (100 mg) were added, and the mixture was stirred at room temperature for 1 h. The mixture was washed successively with 2 N 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), 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 2 N HCl, H_2O, saturated $NaHCO_3$ solution, and brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on a silica gel column (AcOEt−hexane = 1:2) to afford (+)-**32** (8.0 g, 94%) as a pale yellow solid: mp 79−81 °C (colorless prisms from AcOEt−hexane); IR ($CHCl_3$, cm^{-1}) 1746, 1644, 1582; ^1H NMR (200 MHz, $CDCl_3$) δ 2.64 (dd, J = 10, 14 Hz, 1H), 3.01 (dd, J = 5, 14 Hz, 1H), 3.83−3.90 (m, 1H), 3.86 (s, 3H), 3.89 (s, 6H), 3.90 (s, 3H), 4.22−4.36 (m, 2H), 5.93 (s, 2H), 6.28 (d, J = 1.5 Hz, 1H), 6.33 (d, J = 1.5 Hz, 1H), 6.77 (s, 2H), 7.51 (d, J = 1.7 Hz, 1H); MS *m/z* 428 (M^+), 263 (100); $[\alpha]^{24}_D$ +67.5° (*c* 0.835, $CHCl_3$). Anal. Calcd for $C_{23}H_{24}O_8$: C, 64.48; H, 5.65. Found: C, 64.20; H, 5.66.

(3a*S*,*R*-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 ((−)-33) and (3a*S*,*R*-Biar)-3a,4-dihydro-6,9,10,11-tetramethoxy-7,8-(methylenedioxy)dibenzo[4,5:6,7]cycloocta[1,2-*c*]furan-1(3*H*)-one ((−)-34). A mixture of (+)-**32** (50 mg, 0.117 mmol), $Fe(ClO_4)_3 \cdot 6H_2O$ (150 mg, 0.324 mmol), and CF_3CO_2H (0.05 mL) in CH_2Cl_2 (0.5 mL) was stirred at room temperature for 3.5 h. The mixture was washed successively with 6 N HCl, H_2O, and saturated $NaHCO_3$ solution and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on a silica gel column (AcOEt−hexane = 1:2) to give (−)-**33** as colorless plates (23 mg 46%) and (−)-**34** as colorless prisms (3.7 mg, 7%): (−)-**33**: mp 220.5−221.5 °C; IR (KBr, cm^{-1}) 2944, 1758, 1674, 1620, 1594; ^1H NMR (see Table 1); MS *m/z* 426 (M^+, 100); $[\alpha]^{27}_D$ −329° (*c* 1.165, $CHCl_3$). Anal. Calcd for $C_{23}H_{22}O_8$: C, 64.78; H, 5.20. Found: C, 64.60; H, 5.01. (−)-**34**: mp 179.0−180.0 °C; IR (KBr, cm^{-1}) 2940, 2908, 1746, 1666, 1642, 1590; ^1H NMR (see Table 1); MS *m/z* 426 (M^+, 100); $[\alpha]^{27}_D$ −359° (*c* 1.10, $CHCl_3$). Anal. Calcd for $C_{23}H_{22}O_8$: C, 64.78; H, 5.20. Found: C, 64.49; H, 5.06.

(S)-(*E*)-3-(3,4-Dihydroxy-5-methoxybenzyl)-2-(3,4,5-trimethoxybenzylidene)butanolide ((+)-35). To a stirred solution of (+)-**32** (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 MeOH (20 mL), and 2 N 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, (+)-**35** was obtained as a colorless amorphous solid (790 mg, 97%): IR ($CHCl_3$, cm^{-1}) 3556, 2940, 1746, 1646, 1620, 1582, 1498, 1462, 1358, 1334, 1034; ^1H NMR (200 MHz, $CDCl_3$) δ 2.60 (dd, J = 10, 14 Hz, 1H), 3.04 (dd, J

= 5, 14 Hz, 1H), 3.83 (s, 3H), 3.89 (s, 6H), 3.90 (s, 3H), 3.78–3.90 (m, 1H), 4.24–4.30 (m, 2H), 5.31 (s, 1H), 5.36 (s, 1H), 6.43 (d, J = 2 Hz, 1H), 6.23 (d, J = 2 Hz, 1H), 6.79 (s, 2H), 7.51 (d, J = 2 Hz, 1H); MS m/z 416 (M^+) 263 (100); HRMS m/z for $C_{22}H_{24}O_8$ (M^+) 416.14702, found 416.14652; $[\alpha]^{27}_D$ +50.3° (c 0.7, $CHCl_3$).

(3a*S*,*R*-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 ((−)-33). A solution of (+)-**35** (4.18 g, 10 mmol), $Fe(ClO_4)_3$·$6H_2O$ (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 2 N HCl, H_2O, saturated $NaHCO_3$ solution, and brine, and dried over $MgSO_4$. After evaporation of solvent, the residue (**36**) was dissolved in 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, and then dried over $MgSO_4$. The evaporation of the solvent and chromatography of the residue on a silica gel column (AcOEt–hexane = 1:1) gave (−)-**33** as a colorless solid (2.66 g, 62% from **35**). The physical data were completely identical to those of previously obtained (−)-**33**.

(7*S*,*R*-Biar)-7,8-Dihydro-6,7-bis(hydroxymethyl)-1,2,3,10-tetramethoxy-11,12-(methylenedioxy)dibenzo[*a*,*c*]-cyclooctene ((−)-37). DIBAH (1.5 M in toluene, 14 mL, 21 mmol) was added to a solution of (−)-**33** (3.0 g, 7.0 mmol) in THF (50 mL), and the mixture was stirred at 0 °C for 15 min. After addition of acetone (20 mL), the mixture was taken up into AcOEt, washed successively with 2 N HCl, H_2O, saturated $NaHCO_3$ solution, and brine, and dried over $MgSO_4$. After evaporation of the solvent, (−)-**37** was obtained as a colorless solid (3.11 g, 100%): mp 179.0–179.5 °C (colorless prisms from AcOEt–hexane); IR (KBr, cm^{-1}) 3480, 3416, 2940, 2884, 1616, 1594; ^1H NMR (200 MHz, $CDCl_3$) δ 1.89 (br, 1H), 2.46 (dd, J = 9, 13 Hz, 1H), 2.60 (br, 1H), 2.80–3.00 (m, 2H), 3.65 (s, 3H), 3.77 (s, 3H), 3.86 (s, 3H), 3.90 (s, 3H), 3.99–4.17 (m, 2H), 3.68–3.93 (m, 2H), 5.94 (d, J = 1.5 Hz, 1H), 5.92 (d, J = 1.5 Hz, 1H), 6.38 (s, 1H), 6.49 (s, 1H), 6.53 (s, 1H); MS m/z 430 (M^+), 412 (100); $[\alpha]^{27}_D$ −166° (c 1.25, $CHCl_3$). Anal. Calcd for $C_{23}H_{26}O_8$: C, 64.17; H, 6.09. Found: C, 63.98; H, 6.09.

(5*S*,6*S*,7*R*,*R*-Biar)-5,6-Epoxy-5,6,7,8-tetrahydro-6,7-bis-(hydroxymethyl)-1,2,3,12-tetramethoxy-10,11-(methylenedioxy)dibenzo[*a*,*c*]cyclooctene ((+)-38). A solution of (−)-**37** (200 mg, 0.47 mmol), $VO(acac)_2$ (5 mg, 0.019 mmol), and t-BuOOH (3.0 M in 2,2,4-trimethylpentane, 0.35 mL, 1.05 mmol) in CH_2Cl_2 (5 mL) was heated under reflux for 40 min, and then 10% aqueous $FeSO_4$ solution was added. After stirring at room temperature for 30 min, the organic layer was separated, washed with H_2O, and dried over $MgSO_4$. After evaporation of the solvent, (+)-**38** was obtained as a colorless solid (191 mg, 92%): mp 202–202.5 °C (colorless plates from AcOEt–hexane); IR (KBr, cm^{-1}) 3408, 2948, 2884, 1618, 1600, 1498, 1478, 1464, 1402, 1334, 1110, 1072, 1058; ^1H NMR (200 MHz, $CDCl_3$) δ 1.38–1.60 (m, 1H), 2.18–2.34 (m, 1H), 2.53 (dd, J = 8, 15 Hz, 1H), 2.77 (dd, J = 10, 15 Hz, 1H), 2.85–3.02 (m, 1H), 3.12 (d, J = 12 Hz, 1H), 3.66 (s, 1H), 3.67 (s, 3H), 3.86 (s, 3H), 3.905 (s, 3H), 3.912 (s, 3H), 3.52–3.65 (m, 2H), 5.97 (d, J = 1.5 Hz, 1H), 5.98 (d, J = 1.5 Hz, 1H), 6.51 (s, 1H), 6.73 (s, 1H); MS m/z 446 (M^+), 44 (100); $[\alpha]^{27}_D$ +12.69° (c 0.52, $CHCl_3$). Anal. Calcd for $C_{23}H_{26}O_9$: C, 61.87; H, 5.87. Found: C, 61.56; H, 5.91.

(6*RS*,7*SR*,*SR*-Biar)-5,6,7,8-Tetrahydro-6-hydroxy-10-(methanesulfonyloxy)-6,7-bis[(methanesulfonyloxy)-methyl]-1,2,3,12-tetramethoxydibenzo[*a*,*c*]cyclooctene (39). Li (15 mg, 2.1 mmol) was added to a solution of (+)-**38** (50 mg, 0.11 mmol) in liquid NH_3 (3 mL), t-BuOH (0.025 mL), and THF (3 mL) at −78 °C, the mixture was stirred at −78 °C for 10 min, and saturated NH_4Cl solution was added. After evaporation of NH_3, the residue was taken up into AcOEt, washed successively with H_2O and brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was dissolved in pyridine (0.5 mL), methanesulfonyl chloride (0.2 mL) was added, and the mixture was stirred at room temperature for 1 h. AcOEt was added, and the mixture was washed successively with 2 N HCl, H_2O, and saturated $NaHCO_3$ solution, and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on a silica gel column (AcOEt–hexane = 2:1) to give **39** as a colorless solid (27 mg, 57%): IR (KBr, cm^{-1}) 3540, 3020, 2940, 1590, 1464, 1354, 1176; ^1H NMR (200 MHz, $CDCl_3$) δ 2.28–2.50 (m, 4H), 2.79–2.80 (m, 2H), 3.06 (s, 3H), 3.14 (s, 3H), 3.25 (s, 3H), 3.64 (s, 3H), 3.75 (s, 3H), 3.89 (s, 3H), 3.92 (s, 3H), 4.02–4.25 (m, 4H), 6.58 (s, 1H), 6.80 (d, J = 2 Hz, 1H), 6.99 (dd, J = 2 Hz, 1H); MS m/z 654 (M^+), 462 (100).

(7*S*,*R*-Biar)-6,7-Bis(acetoxymethyl)-7,8-dihydro-1,2,3,10-tetramethoxy-11,12-(methylenedioxy)dibenzo[*a*,*c*]-cyclooctene ((−)-40). A solution of (−)-**37** (2.9 g, 6.74 mmol) and Ac_2O (10 mL) in pyridine (20 mL) was stirred at room temperature for 16.5 h and was taken up into AcOEt. The solution was washed successively with 6 N HCl, H_2O, saturated $NaHCO_3$ solution, and brine and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on a silica gel column (AcOEt–hexane = 1:2) to give (−)-**40** as a colorless oil (3.20 g, 92%): IR ($CHCl_3$, cm^{-1}) 1736, 1620, 1594; ^1H NMR (200 MHz, $CDCl_3$) δ 2.054 (s, 3H), 2.045 (s, 3H), 2.30–2.52 (m, 1H), 2.86–3.10 (m, 2H), 3.63 (s, 3H), 3.77 (s, 3H), 3.88 (s, 3H), 3.91 (s, 3H), 4.00–4.30 (m, 2H), 4.48 (d, J = 13 Hz, 1H), 4.53 (d, J = 13 Hz, 1H), 5.93 (d, J = 1 Hz, 1H), 5.94 (d, J = 1 Hz, 1H), 6.34 (s, 1H), 6.48 (s, 1H), 6.58 (s, 1H); MS m/z 514 (M^+, 100); HRMS m/z for $C_{27}H_{30}O_{10}$ (M^+) 514.18389, found 514.18429; $[\alpha]^{26}_D$ −155° (c 0.98, $CHCl_3$).

(7*S*,*R*-Biar)-5,6,7,8-Tetrahydro-7-(hydroxymethyl)-1,2,3,10-tetramethoxy-6-methylene-11,12-(methylenedioxy)dibenzo[*a*,*c*]cyclooctene ((+)-41). A mixture of (−)-**40** (3.09 g, 6.0 mmol), HCO_2NH_4 (4.2 g, 67 mmol), and $Pd(PPh_3)_2Cl_2$ (260 mg, 0.37 mmol) in THF (75 mL) was heated under reflux for 16 h. The reaction mixture was taken up into AcOEt, washed successively with saturated $NaHCO_3$ solution and brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was dissolved in MeOH (40 mL) and 1 N aqueous NaOH solution (10 mL, 10 mmol) was added. After stirring at room temperature for 2 h, the mixture was taken up into AcOEt, washed successively with H_2O and brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on a silica gel column (AcOEt–hexane = 1:1) to give (+)-**41** as a colorless solid (2.30 g, 97% from (−)-**40**): mp 183.5–184.5 °C (colorless prisms from AcOEt–hexane); IR (KBr, cm^{-1}) 3516, 2932, 1620, 1598; ^1H NMR (200 MHz, $CDCl_3$) δ 1.38–1.52 (br, 1H), 2.55–2.66 (m, 1H), 2.49 (dd, J = 2, 13 Hz, 1H), 2.76 (dd, J = 5, 13 Hz, 1H), 2.97 (d, J = 12.5 Hz, 1H), 3.04 (d, J = 12.5 Hz, 1H), 3.29 (t, J = 9 Hz, 1H), 3.62–3.78 (m, 1H), 3.58 (s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 3.90 (s, 3H), 4.82 (d, J = 2 Hz, 1H), 5.12 (d, J = 2 Hz, 1H), 5.97 (s, 2H), 6.56 (s, 1H), 6.66 (s, 1H); MS m/z 414 (M^+), 384 (100); $[\alpha]^{27}_D$ +183° (c 0.99, $CHCl_3$). Anal. Calcd for $C_{23}H_{26}O_7$: C, 66.65; H, 6.32. Found: C, 66.59; H, 6.23.

(6*S*,7*R*,*R*-Biar)-Spiro[5,6,7,8-tetrahydro-7-[(methanesulfonyloxy)methyl]-1,2,3,10-tetramethoxy-11,12-(methylenedioxy)dibenzo[*a*,*c*]cyclooctene-6,2′-oxirane] (42) and (6*R*,7*R*,*R*-Biar)-Spiro[5,6,7,8-tetrahydro-7-[(methanesulfonyloxy)methyl]-1,2,3,10-tetramethoxy-11,12-(methylenedioxy)dibenzo[*a*,*c*]cyclooctene-6,2′-oxirane] (43). A solution of (+)-**41** (1.5 g, 3.6 mmol) and OsO_4 (1.0 g, 3.9 mmol) in pyridine (5 mL) was stirred at room temperature for 30 min. After addition of saturated $NaHSO_3$ solution, the mixture was stirred at room temperature for 42 h and extracted with AcOEt. The combined extracts were washed successively with 2 N 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 (20 mL), methanesulfonyl chloride (1.9 mL) and pyridine (5 mL) were added, and the mixture was stirred at room temperature for 2 h and taken up into AcOEt. The mixture was washed successively with H_2O, 2 N HCl, H_2O, saturated $NaHCO_3$ solution, and brine and dried over $MgSO_4$. After evaporation of the solvent, the residue was dissolved in THF (30 mL), NaH (60% in mineral oil, 200 mg, 5 mmol) was added, and the mixture was stirred at room temperature for 30 min. 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, the residue was chromatographed on a silica gel column (AcOEt–

hexane = 1:3) to give (+)-**42** as a colorless solid (1.45 g, 79%) and (+)-**43** as a colorless solid (0.32 g, 17%): (+)-**42**: mp 111–112.5 °C (colorless needles from AcOEt–hexane); IR (KBr, cm^{-1}) 2936, 1618, 1598; ^1H NMR (200 MHz, $CDCl_3$) δ 1.70–1.84 (m, 1H), 2.17 (d, J = 13 Hz, 1H), 2.73–2.75 (m, 2H), 2.78 (d, J = 13 Hz, 1H), 2.84 (d, J = 5 Hz, 1H), 2.94 (d, J = 5 Hz, 1H), 3.04 (s, 3H), 3.56 (s, 3H), 3.88 (s, 3H), 3.89 (s, 6H), 4.10 (dd, J = 7, 10 Hz, 1H), 4.23 (dd, J = 7, 10 Hz, 1H), 5.99 (d, J = 1.5 Hz, 1H), 6.01 (d, J = 1.5 Hz, 1H), 6.51 (s, 1H), 6.53 (s, 1H); MS 508 (M^+), 412 (base); $[\alpha]^{27}_D$ +138° (c 0.935, $CHCl_3$). Anal. Calcd for $C_{24}H_{28}SO_{10}$: C, 56.68; H, 5.55. Found: C, 56.42; H, 5.53. (+)-**43**: 101–101.5 °C (colorless needles from AcOEt–hexane); IR (KBr, cm^{-1}) 2940, 1622, 1596; ^1H NMR (200 MHz, $CDCl_3$) δ 1.72–1.86 (m, 1H), 2.01 (d, J = 13 Hz, 1H), 2.60 (d, J = 13 Hz, 1H), 2.57–2.64 (m, 1H), 2.84–2.99 (m, 3H), 3.05 (s, 3H), 3.57 (s, 3H), 3.84 (s, 3H), 3.88 (s, 3H), 3.89 (s, 3H), 4.19 (t, J = 10 Hz, 1H), 4.42 (dd, J = 4, 10 Hz, 1H), 5.99 (d, J = 1.5 Hz, 1H), 6.01 (d, J = 1.5 Hz, 1H), 6.45 (s, 1H), 6.68 (s, 1H); MS m/z 508 (M^+, 100); $[\alpha]^{27}_D$ +116° (c 1.09, $CHCl_3$). Anal. Calcd for $C_{24}H_{28}SO_{10}$: C, 56.68; H, 5.55. Found: C, 56.52; H, 5.50.

(+)-Gomisin A (2). To a refluxing solution of $LiAlH_4$ in THF (1.0 M, 9 mL, 9 mmol) was added a solution of (+)-**42** (253 mg, 0.5 mmol) in THF (5 mL), and the mixture was heated under reflux for 5 min. After addition of AcOEt, the mixture was washed successively with 2 N HCl, H_2O, saturated $NaHCO_3$ solution, and brine and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on a silica gel column (AcOEt–hexane = 1:3) to give (+)-gomisin A (**2**) as a colorless solid (205 mg, 99%): mp 93–93.5 °C (colorless needles from AcOEt–hexane); IR (KBr, cm^{-1}) 3572, 3536, 2932, 1620, 1596; ^1H NMR (200 MHz, $CDCl_3$) δ 0.82 (d, J = 7 Hz, 3H), 1.25 (s, 3H), 1.78–1.89 (m, 2H), 2.34 (dd, J = 7, 14 Hz, 1H), 2.35 (d, J = 14 Hz, 1H), 2.59 (dd, J = 4, 1.7 Hz, 1H), 2.69 (d, J = 14 Hz, 1H), 3.52 (s, 3H), 3.84 (s, 3H), 3.91 (s, 6H), 5.96 (d, J = 1.5 Hz, 1H), 5.97 (d, J = 1.5 Hz, 1H), 6.48 (s, 1H), 6.62 (s, 1H); MS m/z 416 (M^+), 398 (100); HRMS m/z for $C_{23}H_{28}O_7$ (M^+) 416.18350, found 416.18394; $[\alpha]^{27}_D$ +67.04° (c 1.08, $CHCl_3$). These data were identical to those of natural gomisin A.

(3a*R*,13a*S*,*R*-Biar)-3a,4,13,13a-Tetrahydro-13a-hydroxy-8,9,10,11-tetramethoxy-6,7-(methylenedioxy)dibenzo-[4,5:6,7]cycloocta[1,2-*c*]furan-1(3*H*)-one ((−)-44) and (3a*R*,13a*R*,*R*-Biar)-3a,4,13,13a-tetrahydro-13a-hydroxy-8,9,10,11-tetramethoxy-6,7-(methylenedioxy)dibenzo[4,5:6,7]cycloocta[1,2-*c*]furan-1(3*H*)-one ((+)-45). A mixture of (−)-**33** (236 mg, 0.55 mmol), $Mn(acac)_2$ (25 mg, 0.087 mmol), and $PhSiH_3$ (0.25 mL, 2.0 mmol) in 2-PrOH (15 mL) was stirred at 60 °C under an oxygen atmosphere for 66 h. After the evaporation of the solvent, the residue was chromatographed on a silica gel column (AcOEt–hexane = 1:2) to give (−)-**44** as a colorless solid (166 mg, 67%), (+)-**45** as a colorless oil (26 mg, 11%), and (−)-**33** as a colorless solid (52 mg, 22%): (−)-**44**: mp >260 °C (colorless prisms from AcOEt): IR (KBr, cm^{-1}) 3420, 2980, 2936, 1766, 1620, 1600; ^1H NMR (200 MHz, $CDCl_3$) δ 2.60–2.86 (m, 6H), 3.62 (s, 3H), 3.87 (s, 3H), 3.90 (s, 3H), 3.91 (s, 3H), 3.85–3.96 (m, 1H), 4.38 (dd, J = 8, 9 Hz, 1H), 5.99 (s, 2H), 6.30 (s, 1H), 6.73 (s, 1H); MS m/z 444 (M^+, 100); $[\alpha]^{26}_D$ −37.96° (c 0.485, $CHCl_3$). Anal. Calcd for $C_{23}H_{24}O_9$: C, 62.15; H, 5.44. Found: C, 62.05; H, 5.45. (+)-**45**: IR ($CHCl_3$, cm^{-1}) 3576, 3004, 2968, 2940, 1778, 1618, 1600, 1478, 1464; ^1H NMR (200 MHz, $CDCl_3$) δ 1.60 (br, 1H), 2.08–2.24 (m, 1H), 2.58 (d, J = 14 Hz, 1H), 2.61 (dd, J = 9, 16 Hz, 1H), 2.93 (dd, J = 8, 16 Hz, 1H), 3.43 (d, J = 14 Hz, 1H), 3.70 (s, 3H), 3.80 (s, 3H), 3.84 (s, 3H), 3.89 (s, 3H), 4.00–4.20 (m, 2H), 5.97 (d, J = 1.5 Hz, 1H), 5.99 (d, J = 1.5 Hz, 1H), 6.41 (s, 1H), 6.49 (s, 1H); MS m/z 444 (M^+, 100); HRMS m/z for $C_{12}H_{24}O_9$ (M^+) 444.14203, found 444.14350; $[\alpha]^{25}_D$ +94.4° (c 0.32, $CHCl_3$).

(6*S*,7*R*,*R*-Biar)-5,6,7,8-Tetrahydro-6-hydroxy-6,7-bis-[(methanesulfonyloxy)methyl]-1,2,3,12-tetramethoxy-10,11-(methylenedioxy)dibenzo[*a*,*c*]cyclooctene ((+)-46). To a refluxing solution of $LiAlH_4$ (400 mg, 10.5 mmol) in THF (10 mL) was added a solution of (−)-**44** (471 mg, 1.06 mmol) in THF (10 mL), and the resultant mixture was heated under reflux for 30 min. The reaction was quenched with $Na_2SO_4 \cdot 10H_2O$ and stirred at room temperature for 1 h, and the insoluble material was filtered off. After evaporation of the solvent, the residue was dissolved in pyridine (5 mL), methanesulfonyl chloride (0.5 mL) was added, and the resultant mixture was stirred at 0 °C for 1.5 h. AcOEt was added, and the mixture was washed successively with 2 N HCl, H_2O, saturated $NaHCO_3$ solution, and brine and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on a silica gel column (AcOEt–hexane = 2:1) to give (+)-**46** as a colorless solid (416 mg, 65%): mp 170.5–171.5 °C dec (colorless needles from AcOEt–hexane); IR (KBr, cm^{-1}) 3524, 2940, 1622, 1600, 1478, 1462, 1354, 1176; ^1H NMR (200 MHz, $CDCl_3$) δ 1.67 (br, 1H), 2.25–2.69 (m, 5H), 3.05 (s, 3H), 3.14 (s, 3H), 3.57 (s, 3H), 3.85 (s, 3H), 3.91 (s, 6H), 4.09–4.21 (m, 4H), 5.98 (d, J = 1.5 Hz, 1H), 5.99 (d, J = 1.5 Hz, 1H), 6.54 (s, 1H), 6.64 (s, 1H); MS m/z 604 (M^+), 83 (100); $[\alpha]^{25}_D$ +89.7° (c 0.30, $CHCl_3$). Anal. Calcd for $C_{25}H_{32}S_2O_{13}$: C, 49.66; H, 5.33. Found: C, 49.51; H, 5.53.

(+)-Gomisin A (2). To a refluxing solution of $LiAlH_4$ (100 mg, 2.6 mmol) in THF (5 mL) was added a solution of (+)-**46** (150 mg, 0.25 mmol) in THF (5 mL), and the resultant mixture was heated under reflux for 15 min. The reaction was quenched with $Na_2SO_4 \cdot 10H_2O$ and stirred at room temperature for 1 h, and the insoluble material was filtered off. After evaporation of the solvent, the residue was chromatographed on a silica gel column (AcOEt–hexane = 1:2) to give (+)-gomisin A (**2**) as a colorless solid (76 mg, 74%). The physical data were completely identical to those of natural gomisin A.

(5*S*,6*S*,7*R*,*R*-Biar)-5,6-Epoxy-5,6,7,8-tetrahydro-6,7-bis-[(methanesulfonyloxy)methyl]-1,2,3,10,11,12-hexamethoxydibenzo[*a*,*c*]cyclooctene ((+)-49). A solution of (+)-**21** (702 mg) and methanesulfonyl chloride (0.5 mL, 6.5 mmol) in pyridine (3 mL) was stirred at 0 °C for 1.5 h. The reaction mixture was taken up into AcOEt, washed successively with 2 N HCl, H_2O, saturated $NaHCO_3$ solution, and brine, and dried over $MgSO_4$. Evaporation of the solvent gave (+)-**49** as a colorless solid (822 mg, 92% from **13**): mp 153–153.5 °C (colorless needles from AcOEt); IR (KBr, cm^{-1}) 2940, 1598, 1356; ^1H NMR (200 MHz, $CDCl_3$) δ 1.75–1.90 (m, 1H), 2.45 (dd, J = 9, 15 Hz, 1H), 2.93–3.12 (m, 1H), 3.01 (s, 3H), 3.07 (s, 3H), 3.68 (s, 3H), 3.72 (s, 1H), 3.89 (s, 3H), 3.91 (s, 6H), 3.92 (s, 3H), 4.36 (s, 2H), 4.41 (d, J = 5 Hz, 2H), 6.59 (s, 1H), 6.71 (s, 1H); MS m/z 618 (M^+), 345 (100); $[\alpha]^{25}_D$ +45.8° (c 0.515, $CHCl_3$). Anal. Calcd for $C_{26}H_{34}S_2O_{13}$: C, 50.47; H, 5.54. Found: C, 50.27; H, 5.56.

(5*R*,7*S*,*R*-Biar)-5,6,7,8-Tetrahydro-5-hydroxy-1,2,3,10,11,12-hexamethoxy-7-methyl-6-methylenedibenzo[*a*,*c*]cyclooctene ((+)-48). A mixture of (+)-**49** (822 mg, 1.33 mmol) and NaI (5.0 g, 33.4 mmol) in methyl isobutyl ketone (30 mL) was heated under reflux for 46 h. The reaction mixture was taken up into AcOEt, washed successively with H_2O, saturated $Na_2S_2O_3$ solution, and brine, dried over $MgSO_4$, and evaporated. The residue was dissolved in MeOH (20 mL), Zn (1.0 g) and AcOH (0.5 mL) were added, and the mixture was stirred at room temperature for 48 h. AcOEt was added, and the mixture was washed successively with 2 N HCl, saturated $NaHCO_3$ solution, and brine, dried over $MgSO_4$, and evaporated to give (+)-**48** as a colorless oil (550 mg, 96% from (+)-**49**): IR ($CHCl_3$, cm^{-1}) 3592, 2936, 1596; ^1H NMR (200 MHz, $CDCl_3$) δ 1.15 (d, J = 7 Hz, 3H), 1.61 (br, 1H), 2.43–2.51 (m, 2H), 2.70–2.90 (br, 1H), 3.60 (s, 3H), 3.67 (s, 3H), 3.88 (s, 3H), 3.89 (s, 3H), 3.90 (s, 3H), 3.92 (s, 3H), 4.88 (s, 1H), 4.92 (s, 1H), 5.40 (s, 1H), 6.52 (s, 1H), 7.05 (s, 1H); MS m/z 430 (M^+, 100); HRMS m/z for $C_{30}H_{30}O_7$ (M^+) 430.19915, found 430.1989; $[\alpha]^{25}_D$ +194.7° (c 0.265, $CHCl_3$).

(5*S*,6*R*,7*S*,*R*-Biar)-Spiro[5,6,7,8-tetrahydro-5-(methanesulfonyloxy)-1,2,3,10,11,12-hexamethoxy-7-methyldibenzo[*a*,*c*]cyclooctene-6,2′-oxirane] ((+)-53). A solution of (+)-**48** (220 mg, 0.51 mmol), $VO(acac)_2$ (5 mg, 0.010 mmol), and *t*-BuOOH (3.0 M in 2,2,4-trimethylpentane, 0.3 mL, 0.9 mmol) in CH_2Cl_2 (5 mL) was stirred at room temperature for 30 min. 10% $FeSO_4$ solution was added, and the mixture was stirred at room temperature for 1 h. The organic layer was separated and dried over $MgSO_4$. After evaporation of the solvent, the residue was dissolved in pyridine (4.0 mL), and methanesulfonyl chloride (0.5 mL) was added. The reaction mixture was

stirred at 0 °C for 15 h and quenched by the addition of H_2O. AcOEt was added, and the mixture was washed successively with H_2O, 2 N HCl, H_2O, and saturated $NaHCO_3$ solution and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by chromatography on a silica gel column (AcOEt–hexane = 1:3) to give (+)-**53** as a colorless oil (248 mg, 92% from **48**): IR ($CHCl_3$, cm^{-1}) 2936, 1989, 1488, 1348; ^1H NMR (200 MHz, $CDCl_3$) δ 1.10 (d, J = 7 Hz, 3H), 1.60–1.80 (m, 1H), 2.56–2.62 (m, 3H), 2.96 (s, 3H), 3.14 (d, J = 4 Hz, 1H), 3.59 (s, 3H), 3.68 (s, 3H), 3.895 (s, 3H), 3.901 (s, 3H), 3.92 (s, 3H), 3.93 (s, 3H), 5.48 (s, 1H), 6.53 (s, 1H), 6.73 (s, 1H); MS *m/z* 524 (M^+), 428 (100); HRMS *m/z* for $C_{25}H_{32}SO_{10}$ (M^+) 524.17162, found 524.17180; $[\alpha]^{25}_D$ +131.6° (*c* 0.415, $CHCl_3$).

(+)-Isoschizandrin (3). A solution of (+)-**53** (10 mg, 0.019 mmol) and $NaBH_4$ (10 mg, 0.26 mmol) in DMF (0.5 mL) was heated at 100 °C for 5.5 h. AcOEt was added, and the mixture was washed with H_2O and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on a silica gel column (AcOEt–hexane = 1:1) to give (+)-isoschizandrin (**3**) (4.0 mg, 49%): mp 111–111.5 °C (colorless prisms from AcOEt–hexane); IR ($CHCl_3$, cm^{-1}) 3600, 3004, 2936, 2836, 1596, 1490, 1462, 1402, 1106; ^1H NMR (200 MHz, $CDCl_3$) δ 0.89 (d, J = 7 Hz, 3H), 1.19 (s, 3H), 1.50 (br, 1H), 1.80–1.96 (m, 1H), 2.32 (d, J = 13 Hz, 1H), 2.52–2.54 (m, 2H), 2.82 (d, J = 13 Hz, 1H), 3.56 (s, 3H), 3.57 (s, 3H), 3.876 (s, 3H), 3.88 (s, 3H), 3.89 (s, 6H), 6.54 (s, 1H), 6.61 (s, 1H); MS *m/z* 432 (M^+, 100); $[\alpha]^{24}_D$ +110.5° (*c* 0.405, $CHCl_3$). Anal. Calcd for $C_{24}H_{32}O_7$: C, 66.65; H, 7.46. Found: C, 66.36; H, 7.50. These data were identical to those of natural isoschizandrin.

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