

# Synthesis of Optically Pure Gomisin A and Schizandrin: The First Total Synthesis of Gomisin A and Schizandrin Having Naturally Occurring Configurations†

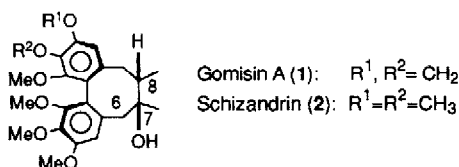
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**Key Words:** Schizandrin; Gomisin A; Iron (III) perchlorate; Optically pure; Natural configurations

**Abstract:** The total synthesis of gomisin A and schizandrin having natural configurations were accomplished for the first time. The key feature of these syntheses is a highly efficient intramolecular oxidative coupling of the intermediates **9** and **21**, which can be obtained as both enantiomers in optically pure forms. The manipulation of the lactone moieties of **7** and **22** afforded natural enantiomers of schizandrin and gomisin A.

Schizandrin (**1**) and gomisin A (**2**) are the main components of lignans isolated from the fruits of *Schisandra chinensis* Baill.(Schisandraceae).<sup>1</sup> In spite of a numerous efforts for the synthesis of related natural products, synthetic study of **1** or **2** were scarcely undertaken and successful total syntheses were limited to racemic or unnatural antipode of **1**.<sup>2</sup> In this paper, we describe the first total synthesis of natural enantiomers of gomisin A and schizandrin.



The synthetic route was shown in Scheme 1. Optically pure half acid **4**,<sup>3</sup> obtained by optical resolution of the salt of racemic **4** and D- $\alpha$ -amino- $\epsilon$ -caprolactam in acetone<sup>4</sup> or asymmetric hydrogenation of **3** (85 %),<sup>5</sup> was converted to **5**<sup>3</sup> by a known procedure (75 %),<sup>6</sup> and by successive aldol condensation-dehydration sequence (LDA, 3, 4, 5-trimethoxybenzaldehyde, -78 °C; Ac<sub>2</sub>O, pyridine, DMAP; DBU, toluene, 70 °C) **5** afforded **6** in 91 % yield. To achieve a construction of biphenyl moiety in **1**, compound **6** was exposed to iron (III) perchlorate in dichloromethane containing trifluoroacetic acid for 3.5 h<sup>7</sup> giving two regioisomeric products (**7**, **8**) in 46% and 7% yields, respectively. Their structures were fully characterized by the aid of the 2D-NOESY experiments assuring not only the regiochemistry but also the relative configurations between C(8) and chiral axis of biphenyl moiety.

To avoid a formation of undesired regioisomer (**8**), numerous reaction conditions were examined, and finally, catechol (**9**), derived from **6** ( $\text{BCl}_3$ ,  $\text{CH}_2\text{Cl}_2$ ;  $\text{HCl}$ ,  $\text{MeOH}$ ; 97 %), was found to afford the desired coupling product **7** regioselectively in 62 % yield by the two steps sequence ( $\text{Fe}(\text{ClO}_4)_3$ ,  $\text{CF}_3\text{CO}_2\text{H}$ ,  $\text{CH}_2\text{Cl}_2$ ;  $\text{CH}_2\text{I}_2$ ,  $\text{K}_2\text{CO}_3$ ,  $\text{DMF}$ ).

With the intermediate (**7**) in hand, transformation of lactone ring to the substituents on C(7) and C(8) of **1** was examined. At first, reductive cleavage of epoxide (**11**), obtained by the reduction and subsequent epoxidation of **7** (DIBAH, THF, 0 °C; *t*-BuOOH,  $\text{VO}(\text{acac})_2$ ,  $\text{CH}_2\text{Cl}_2$ ; 92 %), was attempted, and the product was isolated after mesylation of the reaction mixture ( $\text{Na}$ , liq.  $\text{NH}_3$ , -78 °C;  $\text{MsCl}$ , pyridine; 57 %). But, unfortunately, the only isolable product in this reaction was **12** underscoring the reductive cleavage of the methylenedioxy group on the aromatic ring. After so many fruitless attempts using catalytic hydrogenations or metal hydride reductions, aluminum hydride mediated reductive cleavage of oxirane ring of **11** afforded a desired product (**13**) after mesylation ( $\text{LiAlH}_4$ ,  $\text{AlCl}_3$ ,  $\text{Et}_2\text{O}$ , R.T.;  $\text{MsCl}$ , pyridine, R.T.; 28 %), but the yield of this sequence was only disappointing.

To avoid the reductive cleavage of benzylic carbon-oxygen bond, **10** was converted to **15** in three steps (Scheme 2).<sup>8</sup> Then, introduction of hydroxyl group at C(7) was achieved by osmium tetroxide mediated oxidation giving two isomeric triols, which were separated after the transformation to the mixture of **16** and **17**, in which the major diastereomer (**16**) had the desired stereostructure. Finally, the reductive opening of the oxirane ring and concomitant removal of the mesyloxyl group of **16** with lithium aluminum hydride gave (+)-gomisin A (**1**) in 99 % yield. The physical data of the synthetic gomisin A<sup>3</sup> were in good accord with those of natural one.

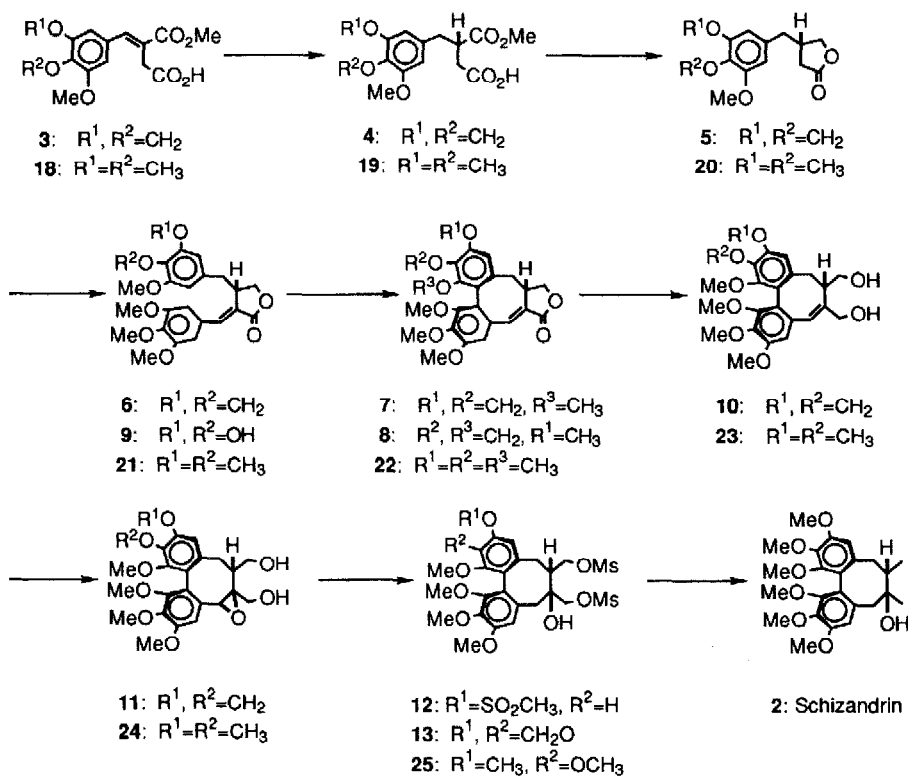
Total synthesis of (+)-schizandrin (**2**) was achieved by the essentially same sequences shown above. Optically pure lactone **20**<sup>3</sup> was obtained by the asymmetric hydrogenation<sup>5</sup> of **18** and subsequent reduction.<sup>9</sup> Compound **21**, obtained by the aldol condensation-dehydration sequence (LDA, 3, 4, 5-trimethoxybenzaldehyde, -78 °C;  $\text{Ac}_2\text{O}$ , pyridine, DMAP; DBU, toluene, 70 °C; 95 %) was oxidatively coupled to **22** ( $\text{Fe}(\text{ClO}_4)_3$ ,  $\text{CF}_3\text{CO}_2\text{H}$ ,  $\text{CH}_2\text{Cl}_2$ , 2h, 90 %).<sup>3,7</sup> After reduction of **22** (DIBAH, THF, 0 °C; 100 %), allylic alcohol **22** was oxidized to give single epoxide **24** (*t*-BuOOH,  $\text{VO}(\text{acac})_2$ ,  $\text{CH}_2\text{Cl}_2$ ; 100 %). In the case of **24**, the reduction with sodium in liquid ammonia was found to cleave the unnecessary C(6)-O bond successively giving dimesylate (**25**) in 45% yield after mesylation of the reaction mixture ( $\text{Na}$ , liq.  $\text{NH}_3$ , -78 °C;  $\text{MsCl}$ , pyridine; 45 %). Finally, by lithium aluminum hydride reduction of **25** in refluxing THF, desired (+)-schizandrin (**2**) was obtained in 91% yield.<sup>3</sup> By a comparison of the physical data of the synthetic and natural schizandrin, the identity of those including absolute configurations were unambiguously demonstrated.

In addition to the above described natural enantiomers, unnatural enantiomers and racemic mixture of **1** and **2** were also synthesized starting from enantiomeric or racemic **4** and **20** by the identical procedure, respectively.<sup>10</sup>

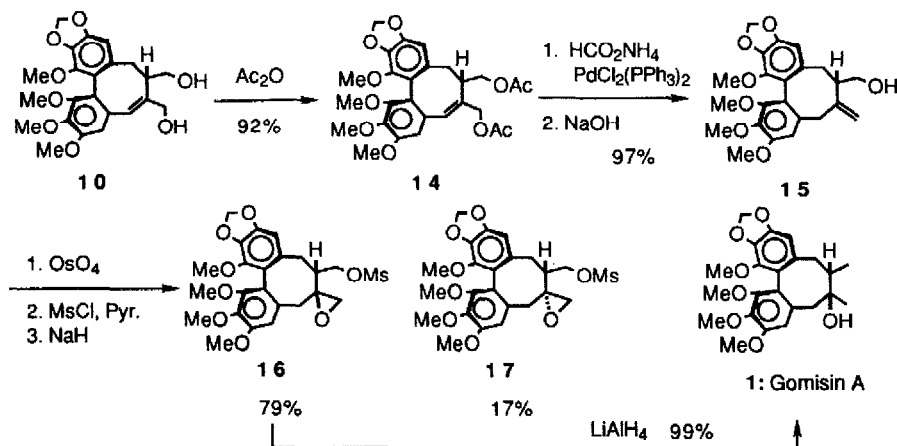
In summary, we succeeded in the first total synthesis of (+)-gomisin A and (+)-schizandrin, in which iron (III) perchlorate mediated biphenyl coupling played an important role for the construction of the molecular skeletons found in those two natural products. The further study to improve the efficiency of the synthesis and the applications of this method to the natural product synthesis having biphenyl moiety are in progress.

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Scheme 1. Synthesis of schizandrin and intermediates for gomisin A



Scheme 2. Synthesis of gomisin A

## REFERENCES AND NOTES

† Dedicated to Emeritus Professor Yoshio Ban and Professor Gilbert Stork on the occasion of their 70th birthday

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- 4: mp 96.5-97.0 °C (colorless prisms from methanol);  $[\alpha]_D^{23}$  -26.6° (c 1.18, CHCl<sub>3</sub>); <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 2.46 (1H, dd, J=4.5, 17Hz), 2.62-2.77 (2H, m), 2.93-3.13 (2H, m), 3.69 (3H, s), 3.88 (3H, s), 5.94 (2H, s), 6.31 (1H, s), 6.34 (1H, s). 5: mp 88.5-89.5 °C (colorless prisms from ethyl acetate);  $[\alpha]_D^{23}$  -6.82° (c 1.12, CHCl<sub>3</sub>); <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 2.27 (1H, dd, J=7, 17Hz), 2.55-2.89 (4H, m), 3.90 (3H, s), 4.03 (1H, t, J=6, 9Hz), 4.34 (1H, dd, J=7, 9Hz), 5.95 (2H, s), 6.30 (1H, d, J=2Hz), 6.34 (1H, d, J=2Hz). 7: mp 220.5-221.5 °C (colorless plates from ethyl acetate-hexanes);  $[\alpha]_D^{27}$  -329° (c 1.165, CHCl<sub>3</sub>); <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 2.43 (1H, d, J=14Hz), 2.99 (1H, dd, J=6, 14Hz), 3.40-3.60 (1H, m), 3.63 (3H, s), 3.81 (3H, s), 3.89 (3H, s), 3.91 (3H, s), 4.44 (1H, t, J=9Hz), 4.09 (1H, dd, J=9, 10Hz), 5.96 (1H, d, J=1.5Hz), 5.98 (1H, d, J=1.5Hz), 6.58 (1H, s), 6.34 (3H, s), 7.51 (1H, d, J=3Hz). 1: mp 93-93.5 °C (colorless needles from ethyl acetate-hexanes);  $[\alpha]_D^{27}$  +67.04° (c 1.08, CHCl<sub>3</sub>); <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 0.82 (3H, d, J=7Hz), 1.25 (3H, s), 1.78-1.89 (2H, m), 2.34 (1H, dd, J=7, 14Hz), 2.35 (1H, d, J=14Hz), 2.59 (1H, dd, J=14, 1.7Hz), 2.69 (1H, d, J=14Hz), 3.52 (3H, s), 3.84 (3H, s), 3.91 (6H, s), 5.96 (1H, d, J=1.5Hz), 5.97 (1H, d, J=1.5Hz), 6.48 (1H, s), 6.62 (1H, s). 20: mp 101.5-103 °C (colorless prisms from ethyl acetate);  $[\alpha]_D^{25}$  -8.50° (c 1.13, CHCl<sub>3</sub>); <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 2.31 (1H, dd, J=7, 17Hz), 2.63 (1H, dd, J=8, 17Hz), 2.71 (2H, d, J=9Hz), 2.79-2.94 (1H, m), 3.84 (3H, s), 3.85 (3H, s), 4.06 (1H, dd, J=6, 9Hz), 4.36 (1H, dd, J=7, 9Hz), 6.36 (2H, s). 22: pale yellow oil;  $[\alpha]_D^{26}$  -284° (c 0.895, CHCl<sub>3</sub>); <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 2.46 (1H, d, J=14Hz), 3.07 (1H, dd, J=7, 14Hz), 3.40-3.60 (1H, m), 3.59 (3H, s), 3.64 (3H, s), 3.88 (3H, s), 3.89 (3H, s), 3.90 (3H, s), 3.92 (3H, s), 4.11 (1H, dd, J=8, 10Hz), 4.47 (1H, t, J=8Hz), 6.41 (1H, s), 6.59 (1H, s), 7.53 (1H, d, J=3Hz). 2: mp 131-132 °C;  $[\alpha]_D^{25}$  +88.0° (c 0.775, CHCl<sub>3</sub>); <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 0.82 (3H, d, J=7Hz), 1.26 (3H, s), 1.80-1.96 (2H, m), 2.37 (1H, d, J=13Hz), 2.38 (1H, dd, J=14, 7Hz), 2.66 (1H, dd, J=14, 2Hz), 2.67 (1H, d, J=13Hz), 3.58 (3H, s), 3.60 (3H, s), 3.88 (3H, s), 3.89 (3H, s), 3.90 (3H, s), 3.91 (3H, s), 6.54 (1H, s), 6.61 (1H, s).
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- Antipodes of natural gomisin A, Schizandrin, and intermediates for them: (+)-4: mp 97.5-98.0 °C (colorless prisms from methanol);  $[\alpha]_D^{23}$  +27.4° (c 0.985, CHCl<sub>3</sub>); <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 2.46 (1H, dd, J=5, 17Hz), 2.62-2.77 (2H, m), 2.93-3.13 (2H, m), 3.69 (3H, s), 3.88 (3H, s), 5.94 (2H, s), 6.31 (1H, s), 6.34 (1H, s). (-)-1: mp 64-65 °C (colorless needles from ethyl acetate-hexanes);  $[\alpha]_D^{27}$  -64.38° (c 1.05, CHCl<sub>3</sub>); <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 0.82 (3H, d, J=7Hz), 1.25 (3H, s), 1.80-1.89 (2H, m), 2.34 (1H, dd, J=7, 14Hz), 2.35 (1H, d, J=14Hz), 2.59 (1H, dd, J=14, 1.7Hz), 2.69 (1H, d, J=14Hz), 3.52 (3H, s), 3.84 (3H, s), 3.91 (6H, s), 5.96 (1H, d, J=1.5Hz), 5.97 (1H, d, J=1.5Hz), 6.48 (1H, s), 6.62 (1H, s). (+)-20: mp 101.5-102.5 °C (colorless prisms from ethyl acetate);  $[\alpha]_D^{25}$  +6.82° (c 1.07, CHCl<sub>3</sub>); <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 2.30 (1H, dd, J=7, 17Hz), 2.57-2.89 (4H, m), 3.83 (3H, s), 3.85 (6H, s), 4.05 (1H, dd, J=6, 9Hz), 4.36 (1H, dd, J=7, 9Hz), 6.36 (2H, s). (-)-2: mp 129.5-131 °C;  $[\alpha]_D^{25}$  -85.28° (c 1.06, CHCl<sub>3</sub>); <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 0.82 (3H, d, J=7Hz), 1.26 (3H, s), 1.80-1.94 (2H, m), 2.37 (1H, d, J=13Hz), 2.38 (1H, dd, J=14, 7Hz), 2.65 (1H, d, J=14Hz), 2.67 (1H, d, J=14Hz), 3.58 (3H, s), 3.59 (3H, s), 3.88 (3H, s), 3.89 (3H, s), 3.90 (3H, s), 3.91 (3H, s), 6.54 (1H, s), 6.61 (1H, s). Racemic gomisin A and schizandrin: (±)-1: mp 165-165.5 °C (colorless needles from ethyl acetate-hexanes); <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 0.82 (3H, d, J=7Hz), 1.25 (3H, s), 1.78-1.89 (2H, m), 2.34 (1H, dd, J=7, 14Hz), 2.35 (1H, d, J=14Hz), 2.59 (1H, dd, J=14, 1.7Hz), 2.69 (1H, d, J=14Hz), 3.52 (3H, s), 3.84 (3H, s), 3.91 (6H, s), 5.96 (1H, d, J=1.5Hz), 5.97 (1H, d, J=1.5Hz), 6.48 (1H, s), 6.62 (1H, s). (±)-2: <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 0.82 (3H, d, J=7Hz), 1.26 (3H, s), 1.75-1.93 (2H, m), 2.30-2.44 (2H, m), 2.56-2.70 (2H, m), 3.58 (3H, s), 3.59 (3H, s), 3.88 (3H, s), 3.889 (3H, s), 3.892 (3H, s), 3.91 (3H, s), 6.54 (1H, s), 6.61 (1H, s).

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