Tetrahedron: Asymmetry Vol. 4, No. 4, pp. 605-608, 1993
Printed in Great Britain

0957-4166/93 $6.00+.00
Pergamon Press Ltd

The Stereoselective First Total Synthesis of Isoschizandrin Having The Natural Configuration

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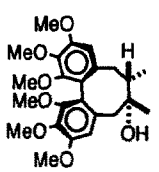
(*Received in UK* 14 *December* 1992; *accepted* 18 *February* 1993)

Key Words: Schisandra chinensis; lignan; optically pure isoschizandrin; structure confirmation; stereoselective synthesis

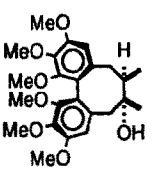
Abstract: *The total synthesis of isoschizandrin* ***1*** *having the natural configuration was accomplished confirming the structure of* ***1*** *in unambiguous manner. Starting from optically pure* ***9****, allylic alcohol* ***11*** *was obtained in good yield, and was then converted into epoxide* ***12*** *stereoselectively. Finally, reductive C-O bond fission afforded the natural enantiomer of isoschizandrin* ***1****.*

The fruits of *Schisandra chinensis* contain a large number of dibenzocyclooctane lignans, the structures of which were elucidated by the extensive work of Ikeya's group.[1] Isoschizandrin is one of the minor components of such dibenzocyclooctanes. At first, the structure of isoschizandrin including the stereochemistry was proposed as **2**, one of the possible three diastereomers of schizandrin **8**, based on the spectroscopic data especially on the NOE data in 1988.[1] In 1990, Meyers reported the synthesis of unnatural enantiomers of four possible diasteromers **1**, **2**, **8**, and **15**, and in that paper, he corrected the strucure of isoschizandrin to **1**, another diastereomer of **8**.[2]

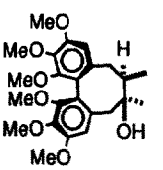
In the course of our study directed toward the synthesis of lignans isolated from *Schisandra chinensis*, we were interested in this structural discrepancy, and we decided to undertake the total synthesis of isoschizandrin having the natural configuration to confirm the actual structure of isoschizandrin in an unambiguous manner. In this paper we report the stereoselective total synthesis and structure confirmation of isoschizandrin **1**.



1 Meyer's proposal



2 originally proposed structure



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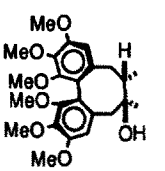
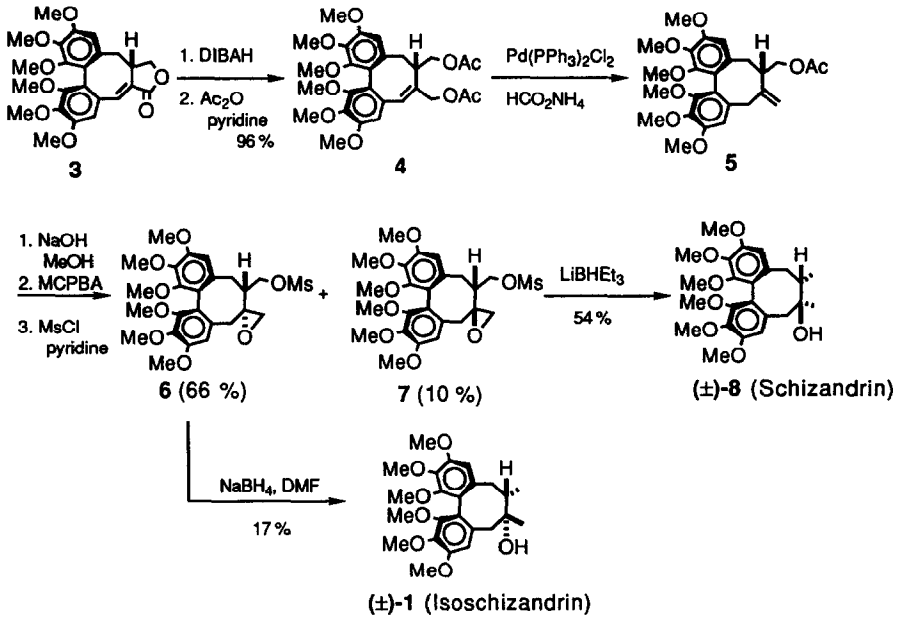
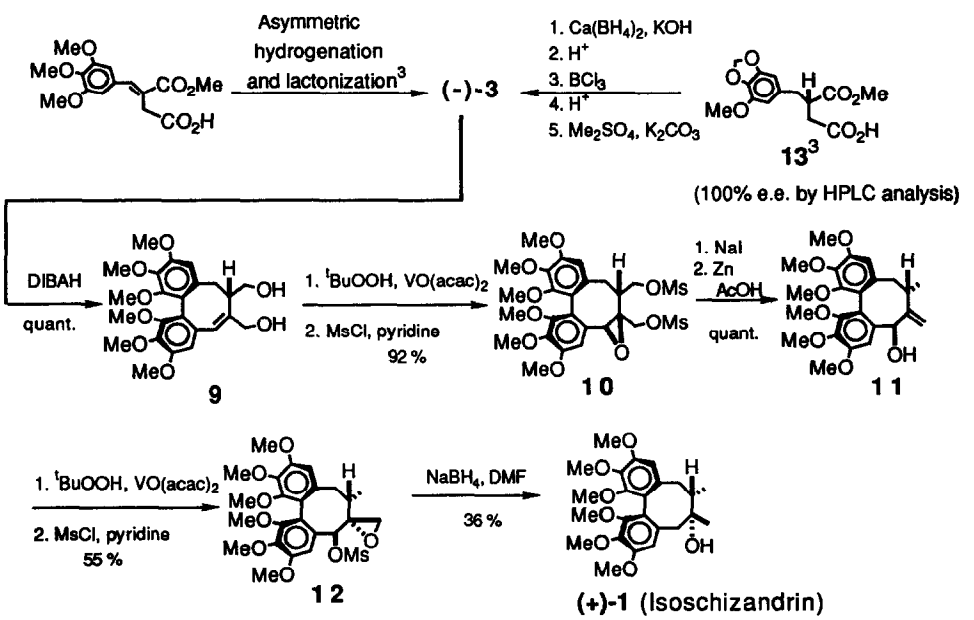


(+)-**8** schizandrin



Scheme 1. Unambiguous confirmation of the structure of (±)-isoschizandrin



Scheme 2. Stereoselective synthesis of optically pure (+)-isoschizandrin

Our preliminary study started with known racemic biphenyllactone 3[3a, b] (Scheme 1). After DIBAH reduction and subsequent acetylation, diacetate 4[4] was reduced with ammonium formate in the presence of bis(triphenylphosphine)palladium dichloride affording the exo-olefinic acetate 5 as a sole product.[4,6] When 5 was successively treated with sodium hydroxide, *m*-chloroperbenzoic acid, and methanesulfonyl chloride, two diastereomeric epoxymesylates 6[4] and 7[4] were isolated in the ratio of 6 : 1, respectively. As the stereostructure of the minor isomer 7 was determined as depicted in the scheme 1 by converting into *dl*-schizandrin 8[5], the stereostructure of major isomer 6 followed unambiguously. The reduction of 6 with sodium borohydride in DMF afforded the mixture of the reduced compounds, and among them, a compound which has the structure proposed by Meyers for isoschizandrin was isolated.

The ^{1}H-NMR and IR spectra of natural isoschizandrin and racemic synthetic specimen obtained as above, were superimposable, and furthermore, the behavior of the natural and synthetic ones on the thin layer chromatography using several solvent systems were indistinguishable. Consequently, we concluded that the exact structure of isoschizandrin must be formulated as 1 in agreement with Meyers.

As the relative stereochemistry of isoschizandrin had been confirmed, we next set about the stereoselective synthesis of optically pure 1 possessing the natural configuration. To this end, we started our synthesis with optically pure (-)-9,[3b,4] which was used in the total synthesis of schizandrin 8 having the natural configuration and can be obtained as optically pure form utilizing Achiwa's asymmetric hydrogenation of an itaconic acid derivative[7] or optically pure succinic acid derivative 13[3] (Scheme 2). By successive treatment with *tert*-butyl hydroperoxide, methanesulfonyl chloride, sodium iodide, and zinc, 9 was transformed into the single allylic alcohol 11 in a stereoselective manner.[4]

As shown in the figure 1, the inspection of the conformational structure of 11, which was obtained by a molecular mechanics calculations,[8] suggested that the hydroxyl group stays below the plane of the exo-methylene double bond. This conformational feature allowed us to utilize this β-oriented hydroxyl group for the stereoselective introduction of the α-oriented tertiary hydroxyl group of isoschizandrin. So, the epoxidation of 11 with *tert*-butyl hydroperoxide in the presence of vanadyl acetylacetonate was attempted. As expected, the reaction proceeded stereoselectively, and, after methanesulfonylation, epoxymesylate 12 was obtained as the only isolable product.[4] Finally, 12 was reduced with sodium borohydride in DMF to give isoschizandrin 1. By comparison of the spectroscopic data and optical rotation data of synthetic (+)-1 with those of natural one, the structure of the synthetic product was confirmed including its absolute configuration.

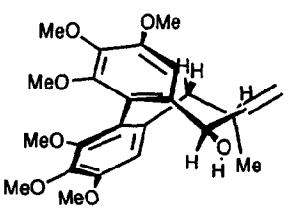


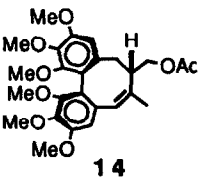
Fig. 1. Conformation of compound 11 obtained by molecular mechanics calculations

Acknowledgement

We are grateful to Dr. Ikeya in our institute for his kind collaboration during the comparison of synthetic and natural isoschizandrin.

References and Notes

1. Ikeya, Y.; Taguchi, H.; Mitsuhashi, H.; Takeda, S.; Kase, Y.; Aburada, M. *Phytochemistry* **1988**, *27*, 569-573 and references cited therein.
2. Warshawsky, A.M.; Meyers, A.I. *J. Am. Chem. Soc.* **1990**, *112*, 8090-8099.
3. (a) Landais, J.; Lebrun, A., *Tetrahedron* **1991**, *47*, 3787-3804. (b) Tanaka, M.; Mukaiyama, C.; Mitsuhashi, H.; Wakamatsu, T. *Tetrahedron Lett.* **1992**, *33*, 4165-4168 and references cited therein.
4. (±)-**4**: mp 127-127.5°C (colorless needles from AcOEt-hexane); ^{1}H-NMR ($CDCl_3$) δ 2.04 (3H, s), 2.05 (3H, s), 2.45 (1H, dd, J=12, 18 Hz), 3.00-3.13 (2H, m), 3.52 (3H, s), 3.66 (3H, s), 3.85 (6H, s), 3.88 (3H, s), 3.91 (3H, s), 4.16 (2H, d, J=7 Hz), 4.48 (1H, d, J=13 Hz), 4.54 (1H, d, J=13 Hz), 6.40 (1H, s), 6.47 (1H, s), 6.59 (1H, s). (±)-**5**: mp 149.5-151 °C (colorless prisms from AcOEt-hexane); ^{1}H-NMR ($CDCl_3$) δ 2.09 (3H, s), 2.52 (1H, d, J=12 Hz), 2.75-2.84 (2H, m), 2.93 (1H, d, J=12 Hz), 3.06 (1H, d, J=12 Hz), 3.61 (3H, s), 3.63 (3H, s), 3.865 (3H, s), 3.869 (3H, s), 3.892 (3H, s), 3.897 (3H, s), 3.96-4.15 (2H, m), 4.81 (1H, d, J=2 Hz), 5.03 (1H, d, J=2 Hz), 6.64 (1H, s), 6.58 (1H, s). (±)-**6**: ^{1}H-NMR ($CDCl_3$) δ 1.72-1.90 (1H, m), 2.03 (1H, d, J=13 Hz), 2.60-2.69 (2H, m), 2.88-3.02 (3H, m), 3.04 (3H, s), 3.61 (6H, s), 3.88 (3H, s), 3.89 (3H, s), 3.90 (3H, s),3.95 (3H, s), 4.23-4.33 (2H, m), 6.45 (1H, s), 6.81 (1H, s). (±)-**7**: ^{1}H-NMR ($CDCl_3$) δ 1.70-1.84 (1H, m), 2.19 (1H, d, J=14 Hz), 2.75 (1H, d, J=14 Hz), 2.84 (1H, d, J=5 Hz), 2.92 (1H, d, J=5 Hz), 2.79-2.86 (2H, m), 3.03 (3H, s), 3.61 (3H, s), 3.64 (3H, s), 3.88 (3H, s), 3.90 (3H, s), 3.91 (3H, s), 3.92 (3H, s), 4.08 (1H, dd, J=7, 10 Hz), 4.29 (1H, dd, J=8, 10 Hz), 6.50 (1H, s), 6.66 (1H, s). (±)-**1**: ^{1}H-NMR ($CDCl_3$) δ 0.89 (3H, d, J=7 Hz), 1.19 (3H, s), 1.57 (1H, s), 1.80-1.96 (1H, m), 2.35 (1H, d, J=15 Hz), 2.50-2.58 (2H, m), 2.84 (1H, d, J=15 Hz), 3.56 (3H, s), 3.57 (3H, s),3.88 (3H, s), 3.880 (3H, s), 3.89 (6H, s), 6.54 (1H, s), 6.61 (1H, s). (-)-**9**: $[\alpha]_D^{27}$ -175 (*c* 0.854, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.90 (1H, br), 2.51 (1H, dd, J=13, 18 Hz), 2.70 (1H, br), 2.96-3.06 (2H, m), 3.52 (3H, s), 3.68 (3H, s), 3.84 (6H, s), 3.87 (3H, s), 3.91 (3H, s), 3.60-4.00 (2H, m), 4.09 (1H, d, J=12 Hz), 4.16 (1H, d, J=12 Hz), 6.43 (1H, s), 6.48 (1H, s), 6.54 (1H, s). (+)-**10**: mp 153-153.5°C (colorless needles from AcOEt); $[\alpha]_D^{25}$ +45.8 (*c* 0.515, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.75-1.90 (1H, m), 2.45 (1H, dd, J=9, 15 Hz), 2.93-3.12 (1H, m), 3.01 (3H, s), 3.07 (3H, s), 3.68 (3H, s), 3.72 (1H, s), 3.89 (3H, s), 3.91 (6H, s), 3.92 (3H, s), 4.36 (2H, s), 4.41 (2H, d, J=5 Hz), 6.59 (1H, s), 6.71 (1H, s). (+)-**11**: $[\alpha]_D^{25}$ +194.7 (*c* 0.265, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.15 (3H, d, J=7 Hz), 1.61 (1H, br), 2.43-2.51 (2H, m), 2.70-2.90 (1H, br), 3.60 (3H, s), 3.67 (3H, s), 3.88 (3H, s), 3.89 (3H, s), 3.90 (3H, s), 3.92 (3H, s), 4.88 (1H, s), 4.92 (1H, s), 5.40 (1H, s), 6.52 (1H, s), 7.05 (1H, s). (+)-**12**: $[\alpha]_D^{25}$ +131.6 (*c* 0.415, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.10 (3H, d, J=7 Hz), 1.60-1.80 (1H, m), 2.56-2.62 (3H, m), 2.96 (3H, s), 3.14 (1H, d, J=4 Hz), 3.59 (3H, s), 3.68 (3H, s), 3.895 (3H, s), 3.901 (3H, s), 3.92 (3H, s), 3.93 (3H, s), 5.48 (1H, s), 6.53 (1H, s), 6.73 (1H, s). (+)-**1**: $[\alpha]_D^{25}$ +100.1 (*c* 0.705, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 0.89 (3H, d, J=7 Hz), 1.19 (3H, s), 1.50 (1H, brs), 1.80-1.96 (1H, m), 2.32 (1H, d, J=13 Hz), 2.52-2.54 (2H, m), 2.82 (1H, d, J=13 Hz), 3.56 (3H, s), 3.57 (3H, s), 3.876 (3H, s), 3.88 (3H, s), 3.89 (6H, s), 6.54 (1H, s), 6.61 (1H, s). Natural (+)-1: $[\alpha]_D^{25}$ +92 (*c* 1.22, $CHCl_3$).[1]
5. By the chemical correlation with 4-bromogomisin A, the structure of which was unambiguously determined by X ray crystallography, the correctness of the structure of **8** had been assured. See Xu, C.-F.; He, C.-H; Pao, Q.-H.; Zheng, Q.-T, *Kezue Tongbao* **1980**, *25*, 1004-1006 and ref. 1.
6. Compound **5** was the only isolable product in this transformation. Compounds with aromatic ring conjugated endo-olefin like **14** could not be detected. See Tsuji, J.; Yamakawa, T. *Tetrahedron Lett.* **1979**, 613-616.
7. Morimoto, T.; Chiba, M.; Achiwa, K. *Tetrahedron Lett.* **1989**, *30*, 735-738.
8. 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).



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