THE FIRST TOTAL SYNTHESIS OF γ-SCHIZANDRIN AND GOMISIN N HAVING NATURAL CONFIGURATIONS

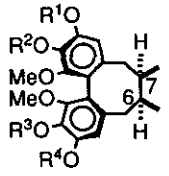
Masahide Tanaka, Toshihiro Ohshima, Hiroshi Mitsuhashi, Masao Maruno, and Takeshi Wakamatsu*

Central Research Laboratories, Tsumura & Co.

3586 Yoshiwara, Ami-machi, Inashiki-gun, Ibaraki 300-11, Japan

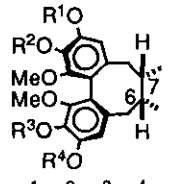
Abstract - The total syntheses of γ-schizandrin and gomisin N were achieved in a stereoselective manner. The success of these synthesis heavily depends on the stereoselective reduction of tetracyclic lactones with magnesium in methanol.

Lignan is the one of the most widely occurring natural products families, and the synthesis of them has been attracting the interest of synthetic chemists for their structural diversity and biological significance.[1] The Chinese folk medicine "gomisi", the fruits of *Schisandra chinensis*, is known to contain a large number of structurally related dibenzocyclooctene lignans,[2] and among them, the syntheses of deoxyschizandrin (**1**) and wuweizisu C (**2**), the major components of "gomisi", have been reported by several groups.[3] However, as to the structurally closely related lignans γ-schizandrin (**3**) or gomisin N (**4**),[2] the other major components, the total synthesis still remains unattained. Probably, it is because the methodologies utilized for the synthesis of **1** or **2** could not be employed for the stereoselective synthesis of **3** or **4**.[3] The brief survey of the structures of **3** and **4** reveals that



1: R^1=R^2=R^3=R^4=Me;
(+)-deoxyschizandrin
(antipode was shown in figure)

3: R^1, R^2=CH_2, R^3=R^4=Me;
γ-schizandrin (racemic mixture)



2: R^1, R^2=R^3, R^4=CH_2;
(-)-wuweizisu C

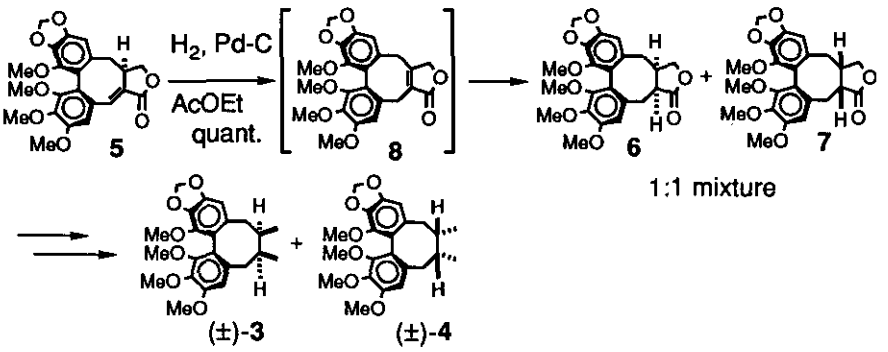
4: R^1, R^2=CH_2, R^3=R^4=Me;
(-)-gomisin N

they are diastereomeric each other, *i.e.*, **3** (occurs in racemic form) possesses the *6S*, 7R*, Sbiar** configurations, while **4** possesses *6R, 7S, Sbiar* ones. For the synthetic routes, which were employed in the total synthesis of **1** or **2**,[3] it seems difficult to introduce the C6 and C7 stereocenters stereoselectively, and those methodologies would lead to the mixture of **3** and **4**.

As the part of our research program directed toward the stereoselective total synthesis of the lignans isolated from *Schisandra chinensis*,[4] we engaged in the synthetic work of **3** and **4**. In this paper, we report the first total synthesis of **3** and **4** in the naturally occurring forms, which succeeded in the stereoselective introduction of C6 and C7 stereocenters.

At first, the synthesis of (±)-γ-schizandrin (**3**) was attempted following the route which was employed for the synthesis of deoxyschizandrin (**1**),[5] *i.e.*, the hydrogenation of readily available tetracyclic α,β-unsaturated lactone (**5**), which was utilized in the total synthesis of gomisin A,[4] followed by the reduction of lactone moiety to dimethyl groups. However, it was soon turned out that the catalytic hydrogenation of **5** was not suitable for the stereoselective transformation. Although the reaction proceeded in the *cis* selective manner, the product was the inseparable mixture of two diastereomeric *cis* lactones (**6**) and (**7**) due to the intermediacy of the butenolide (**8**) (Scheme 1).

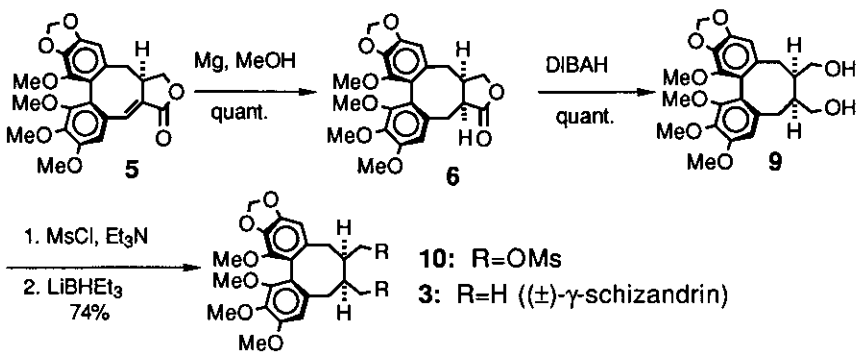
Scheme 1



To avoid the undesired double bond migration, the reduction with magnesium metal[6] was used. In contrast to the palladium catalyzed hydrogenation, reduction of **5** with magnesium in methanol afforded the single lactone (**6**) stereoselectively (Scheme 2). To our delight, possible isomer with *trans* ring juncture could not be detected in the reaction mixture. Then, the transformation of lactone ring to dimethyl groups was achieved uneventfully. Lithium aluminum hydride reduction followed by methanesulfonylation afforded dimesylate (**10**), which was reduced with lithium triethylborohydride providing (±)-γ-schizandrin (**3**) as a single isomer. The mp (128-

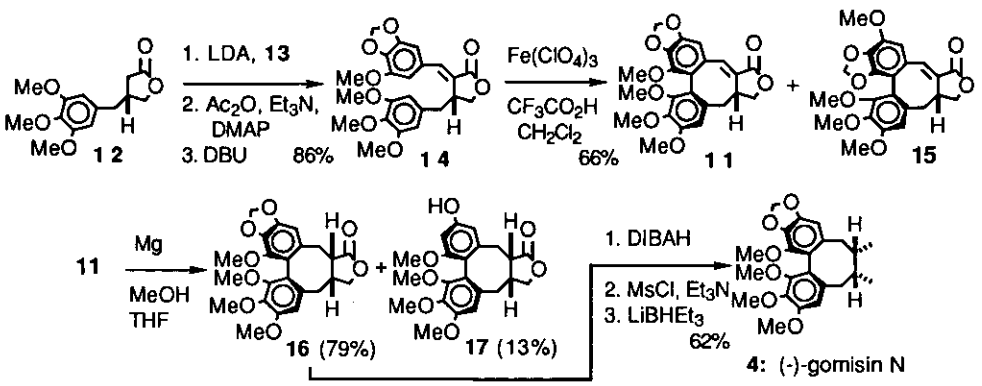
129.5°C) and spectroscopic data (^{1}H-nmr, ir, and ms) of synthetic **3** were identical with those of natural one (mp 126.5-128°C).[2]

Scheme 2



Encouraged with successful synthesis of **3**, the synthesis of (-)-gomisin N (**4**) was set about (Scheme 3). Taking the isomeric nature of **4** with **3** into account, the synthesis was designed to utilize the lactone (**11**) as an intermediate. The aldol condensation of known butyrolactone (**12**)[4] with 3,4-methylenedioxy-5-methoxybenzaldehyde (**13**) followed by dehydration afforded **14** in good yield. Ferric perchlorate mediated oxidative coupling reaction[7] explored by us proceeded as expected providing the desired compound (**11**) as the major product accompanied with small amount of regioisomer (**15**) (66 %, **11**:**15**=*ca.* 8:1). The reduction of the double bond of **11** with magnesium afforded the desired product (**16**) as the major one and the phenolic byproduct (**17**), produced by the reductive cleavage of methylenedioxy group and subsequent hydrogenation of double bond (Scheme 4). Finally, the aforementioned transformation of lactone ring to dimethyl groups furnished (-)-gomisin N (**4**) uneventfully. The mp (102-103.5°C), optical rotation ($[\alpha]_D^{26}$ -82° (c=0.32, $CHCl_3$), and spectroscopic data (^{1}H-nmr, ir, and ms) of synthetic **4** were in good accord with those of natural

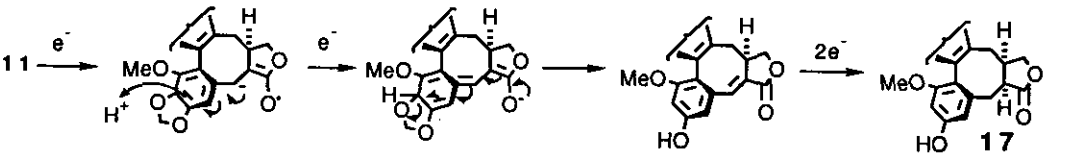
Scheme 3



one (mp 105-107°C, $[\alpha]_D^{23}$ -84.7° ($CHCl_3$)),[2] and the careful inspection of ^{1}H-nmr spectrum assured the absence of γ-schizandrin (**3**), the diastereomer of **4**.

In conclusion, the syntheses of γ-schizandrin and gomisin N were achieved in stereoselective manner. The methodology described here seems useful for the synthesis of wide variety of dibenzocyclooctene lignans and the researches on this line is now underway.

Scheme 4



ACKNOWLEDGMENT

We are grateful to Dr. Ikeya in our institute for his kind advises.

REFERENCES AND NOTES

1. D. A. Whiting, *Nat. Prod. Rep.*, 1985, **2**, 191; D. A. Whiting, *Nat. Prod. Rep.*, 1987, **4**, 499; W. D. MacRae and G. H. N. Towers, *Phytochemistry*, 1984, **23**, 1207; D. C. Ayres and J. D. Loike, 'Chemistry & Pharmacology of Natural Products: Lignans; Chemical, Biological and Clinical Properties', ed. by J. D. Phillipson, Cambridge University Press, Cambridge, 1990.
2. Y. Ikeya, H. Taguchi, I. Yoshioka, and H. Kobayashi, *Chem. Pharm. Bull.*, 1979, **27**, 2695; Y. Ikeya, H. Taguchi, and I. Yoshioka, *Chem. Pharm. Bull.*, 1982, **30**, 132.
3. T. Takeya, T. Ohkubo, S. Nishida, and S. Tobinaga, *Chem. Pharm. Bull.*, 1985, **33**, 3599; E. Ghera, Y. B. David, and D. Becker, *Tetrahedron Lett.*, 1977, 463; N. K. Kochetkov, A. Khorlin, and O. S. Chizhov, *Tetrahedron Lett.*, 1962, 361; T. Biftu, B. G. Hazra, and R. Stevenson, *J. Chem. Soc., Chem. Commun.*, 1979, 2276; G. E. Schneiders and R. Stevenson, *J. Org. Chem.*, 1981, **46**, 2969; Y. Landais, J.-P. Robin, and A. Lebrun, *Tetrahedron*, 1991, **47**, 3787.
4. M. Tanaka, C. Mukaiyama, H. Mitsuhashi, and T. Wakamatsu, *Tetrahedron Lett.*, 1992, **33**, 4165; M. Tanaka, H. Itoh, H. Mitsuhashi, M. Maruno, and T. Wakamatsu, *Tetrahedron Asymmetry*, 1993, **4**, 605.
5. M. Tanaka, H. Mitsuhashi, M. Maruno, and T. Wakamatsu, in preparation.
6. I. K. Youn, G. H. Yon, and C. S. Pak, *Tetrahedron Lett.*, 1986, **27**, 2409.
7. M. Tanaka, H. Mitsuhashi, and T. Wakamatsu, *Tetrahedron Lett.*, 1992, **33**, 4161.

Received, 4th October, 1993