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A New Stereocontrolled Synthesis of Axial-equatorial Furofuran Lignans Having Two Different Aryl Groups: A Synthesis of Fargesin

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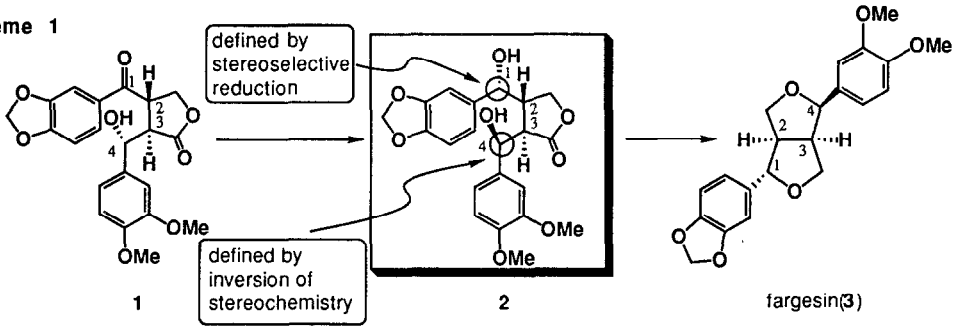
Abstract: Fargesin, a representative example of the axial-equatorial furofuran lignans, was synthesized in a good overall yield based on a new method for inversion of the stereochemistry at C-4 of **1**.

Lignans of the furofuran series are of increasing interest recently because of their intriguing biological activities. In nature have been found two types of furofuran lignans, diequatorial and axial-equatorial ones. However, no stereocontrolled synthesis of this series of lignans having two different aryl groups has been achieved.[1] In the preceding paper, we reported a new stereocontrolled synthesis of the diequatorial furofuran lignans. In this paper, we report a new stereocontrolled synthesis of the axial-equatorial furofuran lignans having two different aryl groups. Our strategy for the synthesis of fargesin (**3**), a representative example of the axial-equatorial furofuran lignans, involves the inversion of the stereochemistry at C-4 of **1** which was obtained in the synthesis of methyl piperitol in the preceding paper.

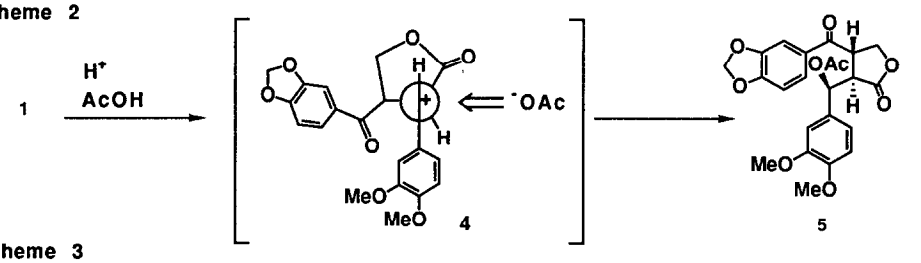
Scheme 1



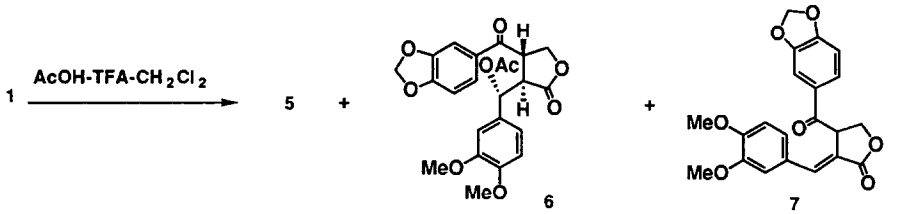
In the preceding paper, we reported the tandem Michael addition-aldol reaction using zinc enolate leading to **1** with a high C-4 *syn*-selectivity. In spite of our intensive investigation, however, the C-4 *anti*-selectivity was not realized in this type of tandem reaction. Furthermore, we could not succeed in the inversion of the stereochemistry at C-4 of **1** based on an SN 2 type reaction; attempts to inverse the stereochemistry at C-4 of **1** using the Mitsunobu reaction were unsuccessful. We anticipated that the inversion of the stereochemistry at C-4 of **1** would proceed effectively *via* the carbonium ion (**4**); the nucleophilic attack of an acetate anion on **4** would take place preferentially from the opposite side of the bulky 3,4-methylenedioxybenzoyl group in the Felkin-like model to produce the *anti*-isomer (**5**) (Scheme 2). Thus, we examined the inversion of the stereochemistry at C-4 of **1** *via* **4**. Treatment of **1** with a mixture of acetic acid, trifluoroacetic acid (TFA)

and CH_2Cl_2 at 0 °C gave a mixture of **5**[2], **6** and **7** (Scheme 3). The yield of **5** changed depending on both the reaction time and the ratio of the solvents used.[3] The best result was obtained by treatment of **1** with a mixture of TFA, AcOH and CH_2Cl_2 (1:10:1) for 11 h, the isolated yield of **5** being 62%.

Scheme 2

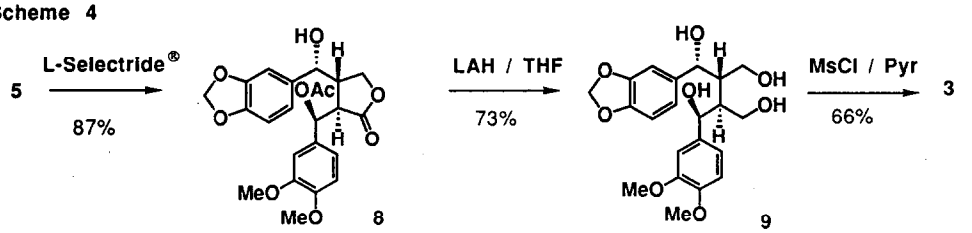


Scheme 3



We next examined the conversion of **5** into fargesin (**3**). Reduction of **5** with L-Selectride® in THF at -50 °C afforded **8**[5] in 87% yield, the ratio of **8** to the corresponding isomer being 98:2. **8** was reduced with lithium aluminium hydride (LAH) in THF to afford **9**[6] in 73% yield. Treatment of **9** with methanesulfonyl chloride in pyridine at room temperature furnished fargesin (**3**)[7] in 66% yield.

Scheme 4



As described above, we achieved the fully stereocontrolled synthesis of fargesin. The present methodology should offer a new entry to the synthesis of the axial-equatorial furofuran lignans having two different aryl groups.

References and Notes:

1. See the references 1-8 of the preceding paper.
2. **5**: mp 135-138 °C; ^{1}H NMR (δ in $CDCl_3$) 2.08 (s, 3H), 3.78 (s, 1H), 3.83 (s, 3H), 3.7-3.9 (m, 2H), 4.0-4.4 (m, 2H), 6.00 (s, 2H), 6.26 (d, 1H, *J*=5.4 Hz), 6.6-7.0 (m 4H), 7.2-7.4 (m, 2H).
3. For example, **5**, **6** and **7** were obtained in 36%, 5% and 41% yields, respectively in TFA-AcOH-CH_2Cl_2 (1:1:1) at 0 °C for 6 h. In TFA-AcOH-CH_2Cl_2 (1:20:1) at 0 °C for 6 h, **5** and **6** were obtained in 18% and 3% yields, respectively; in this reaction, **1** was recovered in 55% yield.
4. **6**: mp 138-140 °C; ^{1}H NMR (δ in $CDCl_3$) 2.06 (s, 3H), 3.79 (s, 1H), 3.82 (s, 3H), 3.8-3.9 (m, 1H), 4.0-4.7 (m, 3H), 6.06 (s, 2H), 6.26 (d, 1H, *J*=3.4 Hz), 6.6-6.9 (m 4H), 7.10 (d, 1H, *J*=1.6 Hz), 7.25 (dd, 1H, *J*=1.6, 11.4 Hz).
5. **8**: mp 156-158 °C;^{1}H NMR (δ in DMSO-d_6) 2.04 (s, 3H), 2.5-2.9 (m, 2H), 3.76 (s, 3H), 3.88 (s, 3H), 4.2-4.6 (m, 3H), 4.9-5.3 (m, 2H), 5.97 (s, 2H), 6.2-6.8 (m, 6H).
6. **9**: mp 134 °C; ^{1}H NMR (δ in DMSO-d_6) 1.8-2.2 (m, 2H), 3.2-3.8 (m, 4H), 3.60 (s, 3H), 3.70 (s, 3H), 4.5-4.7 (m, 2H), 4.9-5.1 (m, 2H), 5.2-5.5 (m, 2H), 5.92 (s, 2H), 6.3-6.8 (m, 6H).
7. **3**: (+)-fargesin: mp 138-141 °C (lit.[8] 138-139 °C) The ^{1}H NMR, IR and MS spectral data were in accord with those of natural fargesin.
8. Kakisawa, H.; Chen, Y P.; Hsui, H. Y. *Phytochemistry* **1972**, *11*, 2289.

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