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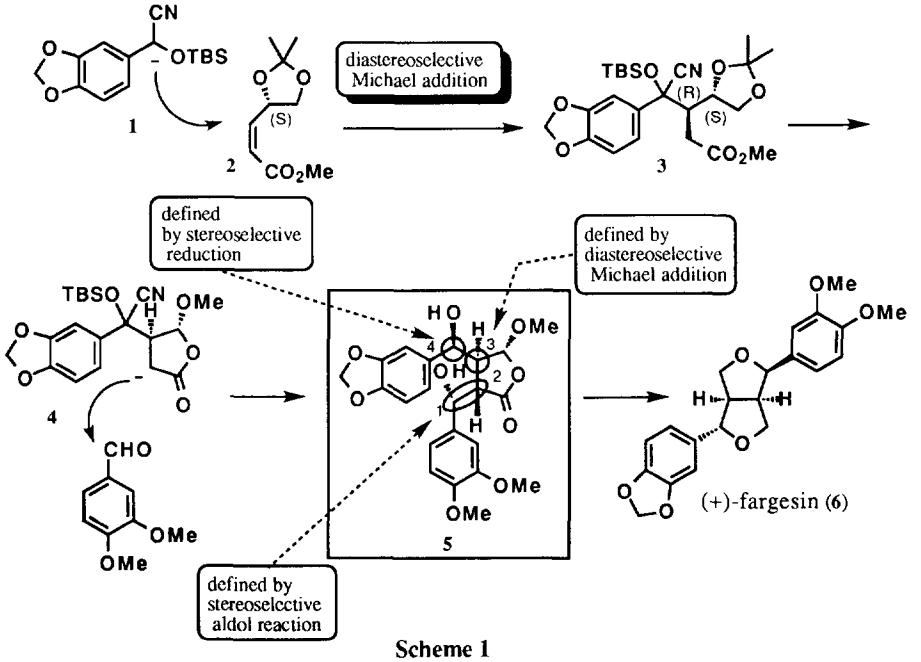
A Novel Asymmetric Synthesis of Axial-Equatorial Furofuran Lignans: A Synthesis of (+)-Fargesin

Shin-ichi Yoshida, Takeshi Yamanaka, Tutomu Miyake, Yasunori Moritani, Hiroshi Ohmizu,* and Tameo Iwasaki

Lead Optimization Research Laboratory, Tanabe Seiyaku Co., Ltd.,
3-16-89 Kashima, Yodogawa, Osaka 532, Japan

Abstract: (+)-Fargesin (**6**), a representative example of the axial-equatorial furofuran lignans having two different aryl groups, was efficiently synthesized based on a highly diastereoselective Michael addition reaction of the cyanohydrin **1** to methyl (*S*)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-*cis*-2-propenoate (**2**).

Lignans of the furofuran series[1,2] are of increasing interest because of their intriguing biological activities.[3] Although much effort has been devoted to developing an efficient method for the synthesis of this series of lignans,[4] only two methods have been reported for the asymmetric synthesis of the lignans; these methods include those based on the diastereoselective hetero Diels-Alder reaction[4g] and a tandem conjugate

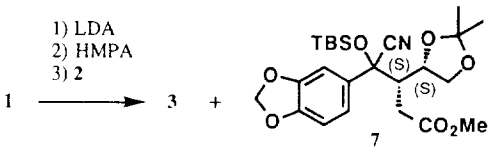


Scheme 1

addition-aldol reaction of the thioacetal to the chiral butenolide.[4i] In connection with our synthetic studies in search of new compounds having interesting biological activities from lignan derivatives,[5] we would like to report herein a novel asymmetric synthesis of (+)-fargesin (**6**), a representative example of the axial-equatorial furofuran lignans, based on a highly diastereoselective Michael addition reaction of the *O*-TBS cyanohydrin **1** to methyl (*S*)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-*cis*-2-propenoate (**2**).[6]

We previously reported the stereocontrolled synthesis of racemic fargesin utilizing the three component reaction of the *O*-TBS cyanohydrin **1**, 2-butenolide and veratraldehyde as a key reaction.[5b] Taking the synthesis into consideration, we planned the strategy for an asymmetric synthesis of (+)-fargesin (**6**). The main features of the strategy are illustrated in Scheme 1. We envisaged that **6** would be synthesized *via* the key intermediate **5**. The four contiguous chiral-carbon centers of **5** would be enantiomerically defined by using the key reactions involving: (i) the diastereoselective Michael addition reaction of **1** to the chiral α,β-unsaturated ester **2**, leading to **3**; (ii) the stereoselective aldol reaction of the γ-lactone **4** and veratraldehyde; (iii) the stereoselective reduction of the carbonyl group at C-4, leading to **5**.

According to the strategy described above, we first examined the diastereoselective Michael addition reaction of the cyanohydrin **1** to **2**. At first, the Michael addition reaction was carried out employing lithium diisopropylamide (LDA) in THF at -78 °C. In this reaction, a mixture of the Michael adducts **3** and **7** was obtained in 73% yield; the diastereoselectivity was, however, only 10% de (Table 1, run 1).[7] In order to obtain higher diastereoselectivity, we examined the reaction under various reaction conditions, and found that the diastereoselectivity was remarkably improved by addition of hexamethylphosphoramide (HMPA) to the reaction mixture. When an equimolar amount of HMPA was used, the Michael adducts were obtained in 88% yield with 74% de (run 2). Furthermore, both the yield and the diastereoselectivity heightened significantly when the reaction was carried out at -100 °C (run 3). In order to optimize the amount of HMPA, the reaction was carried out at -100 °C by using two or three molar equivalents amount of HMPA (run 4 and 5). The diastereoselectivity was improved to be 93% de, whereas the yield lowered slightly with increasing amount of HMPA. Thus, the best result was obtained when the reaction was carried out at -100 °C by using two molar equivalents of HMPA (run 4).

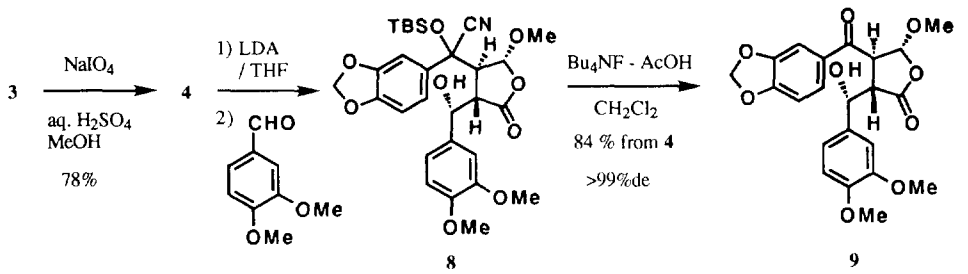


Scheme 2

Table 1

Run	Temp. (°C)	HMPA (eq.)	Combined Yield (%) (3 + 7)	dc(%)*
1	-78	0	73	10
2	-78	1	88	74
3	-100	1	97	80
4	-100	2	94	93
5	-100	3	92	93

* Determined by HPLC analysis of the crude reaction products.

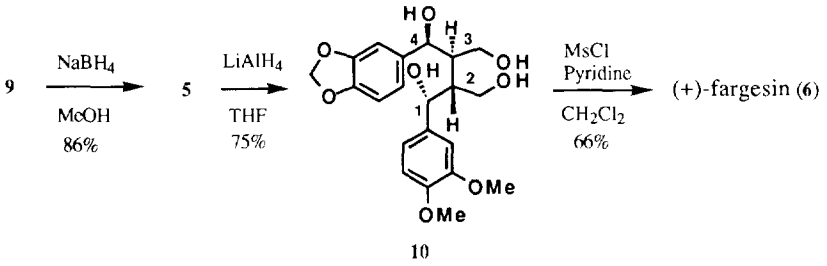


Scheme 3

The Michael adduct **3** thus obtained was next converted into the γ-lactone **4** in 78% yield by treatment with sodium metaperiodate in methanol (Scheme 3).[8)]

The aldol reaction of **4** with veratraldehyde was next examined. The aldol reaction was carried out in THF at -78 °C by using LDA as a base. The product was treated with tetrabutylammonium fluoride (TBAF) in CH_2Cl_2 containing acetic acid to afford **9** in 84% yield as a sole product.[9)] The result obtained in the above aldol reaction was in marked contrast to that observed in the aldol reaction under the same reaction conditions in the syntheses of the racemic furofuran lignans, in which *syn*- and *anti*-isomers were obtained in the ratio of 1:1.[5b)] The presence of the methoxyl group of **4** presumably plays an important role to stabilize the reaction intermediate as the chair-transition structure leading to the *anti*-isomer **9**.

We finally examined conversion of **9** into (+)-fargesin. At first the *anti*-isomer **9** was reduced with $LiAlH_4$. However, no selectivity was observed at C-4 carbon center. This problem was solved by a stepwise reduction. The ketone **9** was first reduced with $NaBH_4$ in methanol at 0°C to afford the diol **5** and its C-4 stereoisomer in 86 and 8% yields, respectively. Then, **5** was further reduced with $LiAlH_4$ in THF to give the tetraol **10** in 75% yield (Scheme 4).[10)] Finally, **10** was converted into (+)-fargesin (**6**) in 66% yield by the method previously reported.[5b,11)]



Scheme 4

As described above, we have achieved a novel asymmetric synthesis of (+)-fargesin. The present method should find wide application in the synthesis of chiral axial-equatorial furofuran lignans.

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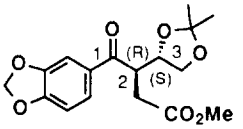
7. The stereochemistries of C-2 of **3** and **7** were determined by converting them into **11** and **12**, respectively. The stereochemistry of the minor product **12** was unambiguously determined based on X-ray crystallographic analysis and the major product **11** was determined to be the isomer of **12** at C-2 by NMR analysis. Crystal data for **12** has been deposited at the Cambridge Crystallographic Data Center.

   11: $[\alpha]_D^{25}$= -43° (C=1.0, $CHCl_3$); IR (film) 1736, 1672 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 1.28 (s, 3H), 1.40 (s, 3H), 2.53 (dd, 1H, *J*=4.1, 16.8Hz), 2.96 (dd, 1H, *J*=9.5, 16.8Hz), 3.62 (s, 3H), 3.78 (dd, 1H, *J*=6.5, 8.6Hz), 3.96 (dd, 1H, *J*=6.5, 8.6Hz), 4.18 (m, 1H), 4.34 (dd, 1H, *J*=6.5, 13.0Hz), 6.05 (s, 2H), 6.88 (d, 1H, *J*=8.2 Hz), 7.49 (d, 1H, 1.7Hz), 7.68 (dd, 1H, *J*=1.7, 8.2Hz).

   12: mp 94~95 °C; $[\alpha]_D^{25}$= +74° (C=1.0, $CHCl_3$); IR (KBr) 1719, 1664 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 1.31 (s, 3H), 1.36 (s, 3H), 2.77 (dd, 1H, *J*=4.7, 16.8Hz), 2.97 (dd, 1H, *J*=8.9, 16.8Hz), 3.62 (s, 3H), 3.63 (dd, 1H, *J*=5.7, 8.6Hz), 3.96 (m, 2H), 4.25 (m, 1H), 6.06 (s, 2H), 6.88 (d, 1H, *J*=8.2 Hz), 7.48 (d, 1H, 1.7Hz), 7.66 (dd, 1H, *J*=1.7, 8.2Hz).



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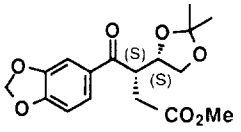

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8. The lactone **4** was a 2:1 mixture of the stereoisomers. The mixture was subjected to the next reaction without separation because both isomers were convertible into (+)-fargesin.
9. **9**: $[\alpha]_D^{20}$= -42° (C=1.0, $CHCl_3$); IR (film) 3503, 1769, 1672 cm^{-1} ;^1H NMR (δ in $CDCl_3$) 3.53 (s, 3H), 3.60 (dd, 1H, *J*=8.5, 8.8Hz), 3.76 (s, 3H), 3.77 (dd, 1H, *J*=4.6, 8.5Hz), 3.78 (s, 3H), 4.88 (d, 1H, *J*=8.8Hz), 5.30 (d, 1H, *J*=4.6Hz), 6.03 (s, 2H), 6.58 (d, 1H, *J*=9.2Hz), 6.69~6.81(m, 3H), 7.02 (d, 1H, *J*=1.8 Hz), 7.15 (dd, 1H, *J*=1.8, 8.2Hz).
10. **5**: mp 139 °C; $[\alpha]_D^{20}$= -84° (C=1.0, $CHCl_3$); IR (KBr) 3419, 1758 cm^{-1} ; ^1H NMR (δ in $CDCl_3$, D_2O exchange) 2.31 (m, 1H), 2.83 (dd, 1H, *J*=4.0, 8.2 Hz), 3.41 (s, 3H), 3.76 (s, 3H), 3.86 (s, 3H), 4.69 (d, 1H, *J*=5.0 Hz), 4.86 (d, 1H, *J*=8.2 Hz), 5.22 (d, 1H, *J*=2.0 Hz), 5.95 (d, 1H, *J*=1.6 Hz), 6.00 (d, 1H, *J*=1.6 Hz), 6.27 (s, 1H), 6.58~6.64 (m, 3H), 6.71 (s, 2H).
11. **6**: mp 135~136°C; $[\alpha]_D^{20}$= +122° (C=1.0, $CHCl_3$). ^1H NMR and IR spectra were in good agreement with those of natural fargesin[12].
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