STEREOCONTROLLED SYNTHESES OF UNSYMMETRICALLY SUBSTITUTED FUROFURAN LIGNANS

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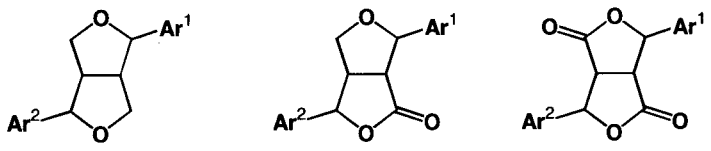
Abstract – Novel and efficient methods for the syntheses of the simple furofuran lignans (I) and the bislactone furofuran lignans (III) are comprehensively described. Asymmetric synthesis of the series (I) based on the enantioselective Michael addition reaction is also described.

Introduction

Furofuran lignans I (3,7-dioxabicyclo[3.3.0]octane), II (4-oxo-3,7-dioxabicyclo[3.3.0]octane) and III (4,8-dioxo-3,7-dioxabicyclo[3.3.0]octane) are of considerable interest because of their wide range of biological activities (Figure 1).[1] Some of naturally occurring simple furofurans (series I) and monolactones (series II) have been reported to exhibit inhibition activity of phosphodiesterases and antagonistic activity of platelet aggregation factor.[2] Some bislactones (series III) have also been known to modulate the function of central nervous systems by inhibition of catechol-*O*-methyltransferase, dopamine β-hydroxylase and dopa decarboxylase.[3] Much effort has been devoted to developing an efficient method for syntheses of the furofuran series of lignans and some ingenious ones have been reported.[4] Four basic methodologies so far employed for the synthesis of this series of lignans involve those based on: (i) the reaction of succinamide dianion with an aromatic aldehyde;[5] (ii) the dimerization of the substituted cinnamic acids;[6] (iii) the cyclization of the silyl enol ether of a lactone;[4c,d,e] (iv) the tandem Michael addition-aldol reaction of a dithiane derivative.[4a,b] However, these methods can not be

applied to the stereocontrolled synthesis of the furofuran lignans having two different aryl groups. On the other hand, only a little attention has been devoted to syntheses of bislactone subgroup III; some nonstereocontrolled syntheses based on the oxidative dimerization of the cinnamic acid derivatives,[7] the reaction of 2,5-bis(trimethylsilyloxy)furans with benzaldehydes,[8] and aldol reaction of *N,N,N',N'*-tetraethylsuccinic diamide with aromatic aldehydes have been reported.[5] In connection with our synthetic studies in search of new compounds having intriguing biological activities from lignans, the authors have been interested in synthesis of furofuran lignans.[9] In this review article, the authors describe stereocontrolled syntheses of the series I based on the three component reaction of a cyanohydrin, 2-butenolide and an aromatic aldehyde, and the series III based on the aldol reaction of a cinnamic anhydride derivative with an aromatic aldehyde.[10] Asymmetric synthesis of the series I based on the enantioselective Michael addition reaction of a cyanohydrin to an α,β-unsaturated ester is also described.[11]



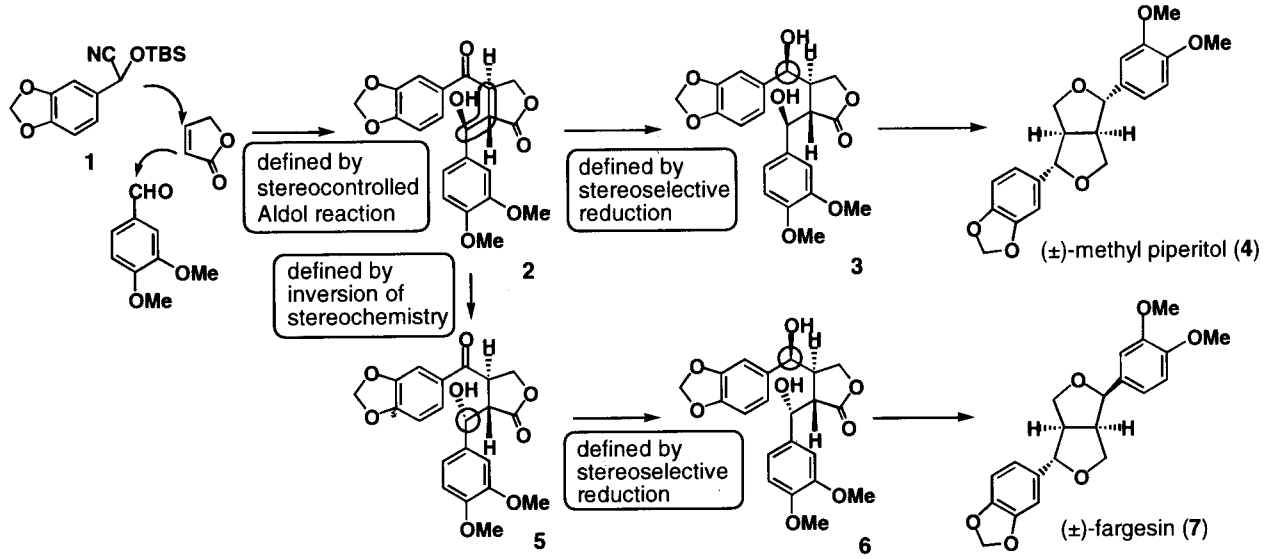
I II III

Figure1

Synthesis of Furofuran Lignans

Two isomers, the equatorial type and the axial-equatorial type, exist in nature. The authors planed a strategy for the stereoselective synthesis of these lignans utilizing **2** as a key intermediate as shown in Scheme 1. Namely, **2** would be obtained by the stereoselective three component joining reaction of the cyanohydrin (**1**), 2-butenolide, and an aldehyde followed by transformation of the cyanohydrin moiety into a carbonyl group. The diequatorial type (**4**) would be selectively synthesized by stereoselective reduction of the carbonyl group of **2** leading to the *syn*-alcohol (**3**) followed by reduction and cyclization. On the other hand, the axial-equatorial type (**7**) would be synthesized in a same manner if inversion of the stereochemistry of the hydroxyl group at C-1 could be achieved.

Scheme 1



Scheme 2

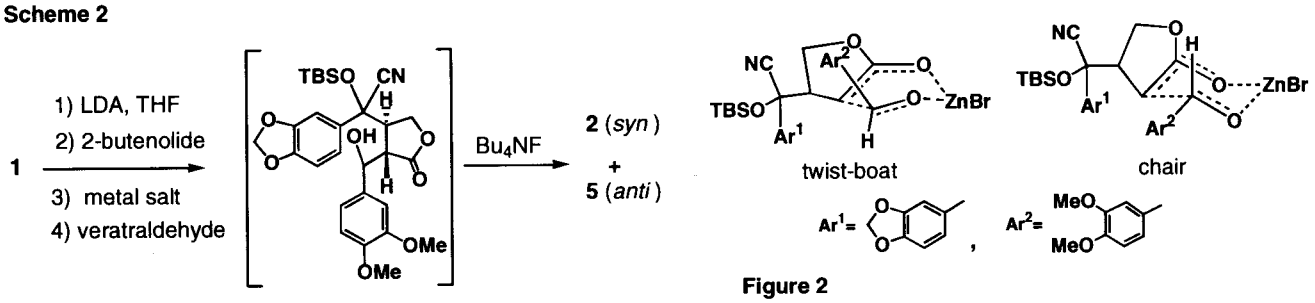
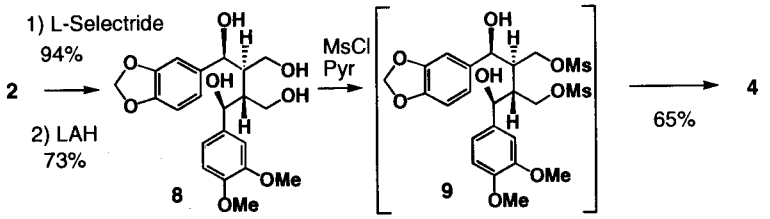


Figure 2

According to this strategy, the three component joining reaction consisted of **1**, 2-butenolide and veratraldehyde was first examined (Scheme 2). When LDA was used as the base, the stereochemistry on C-1 was not controlled and a mixture of the *syn*-isomer (**2**) and the *anti*-isomer (**5**) was obtained in almost 1:1 ratio. It has been generally known that the transition metal counter cation gives higher *syn*-selectivity than lithium cation in aldol reaction of (*E*)-enolate.[12] Thus, the counter cation of the enolate was exchanged from lithium cation to other metal cation by adding $MgBr_2$, $Sn(OTf)_2$, and $ZnBr_2$ etc. As expected, the *syn*-isomer (**2**) was predominantly obtained in 98:2 in the use of $ZnBr_2$. The difference in stability between the twist-boat type transition structure leading to the *syn*-isomer and the chair type transition structure leading to the *anti*-isomer would elucidate the stereoselectivity in the use of $ZnBr_2$ (Figure 2).[13] The *syn*-isomer (**2**) was next stereoselectively reduced by L-Selectride to afford **3**. The

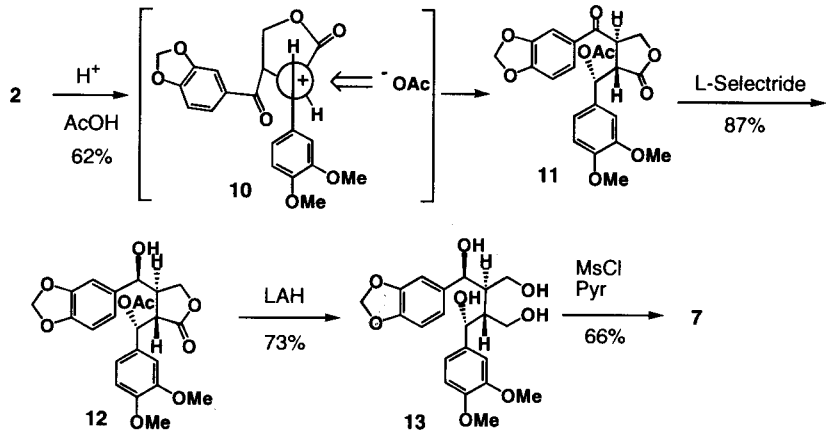
Scheme 3



diol (**3**) was reduced by $LiAlH_4$ to **8** followed by cyclization in the use of MsCl / pyridine to give (±)-methyl piperitol (**4**) (Scheme 3).

On the other hand, the *anti*-isomer (**11**), the key intermediate leading to (±)-fargesin (**7**), would be predominantly obtained, if the acetoxyl anion selectively attack from the sterically less hindered side to the carbocation (**10**) which could be generated from **2** under the acidic conditions. The reaction was examined under various conditions, and **11** was obtained predominantly in 62 % yield by treatment of **2** under TFA-AcOH-CH_2Cl_2 (1:10:1) conditions. The *anti*-isomer (**11**) was reduced in the same manner followed by cyclization to afford (±)-fargesin (**7**) (Scheme 4).

Scheme 4

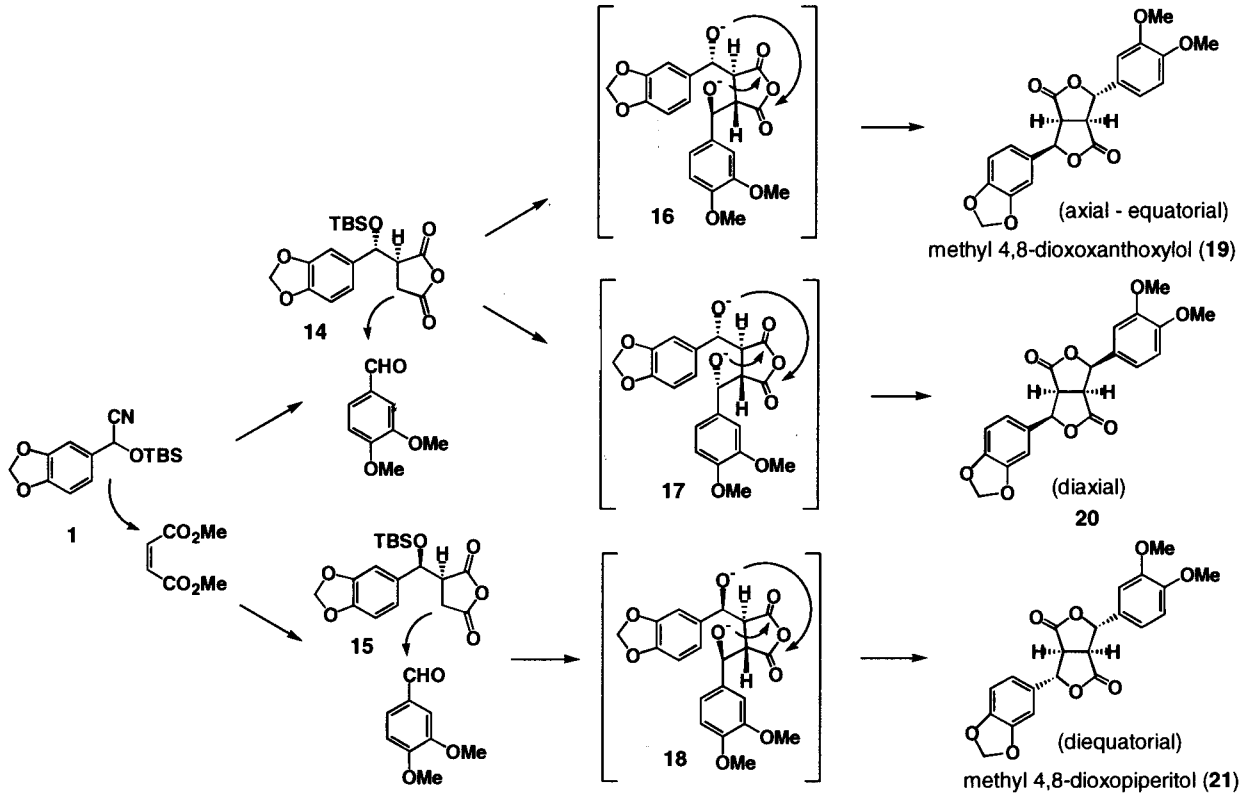


The present method will be applicable to the synthesis of the furofuran lignans having a variety of substituents and be recognized as a general method for the synthesis of the axial-equatorial and diequatorial types of furofuran lignans.

Synthesis of the Bislactone Type Furofuran Lignans

The bislactone type furofuran lignans exist as an analog of the furofuran lignans. Two stereoisomers, the axial-equatorial and the diequatorial types, exist in nature. The stereoselective synthesis of these isomers has not yet been achieved. As shown in Scheme 5, the authors envisaged that this series of lignans including the diaxial type would be synthesized by the stereoselective aldol reaction of the acid anhydrides (**14** and **15**) with an aromatic aldehyde, followed by cyclization of the key intermediate (**16-18**).

Scheme 5



Scheme 6

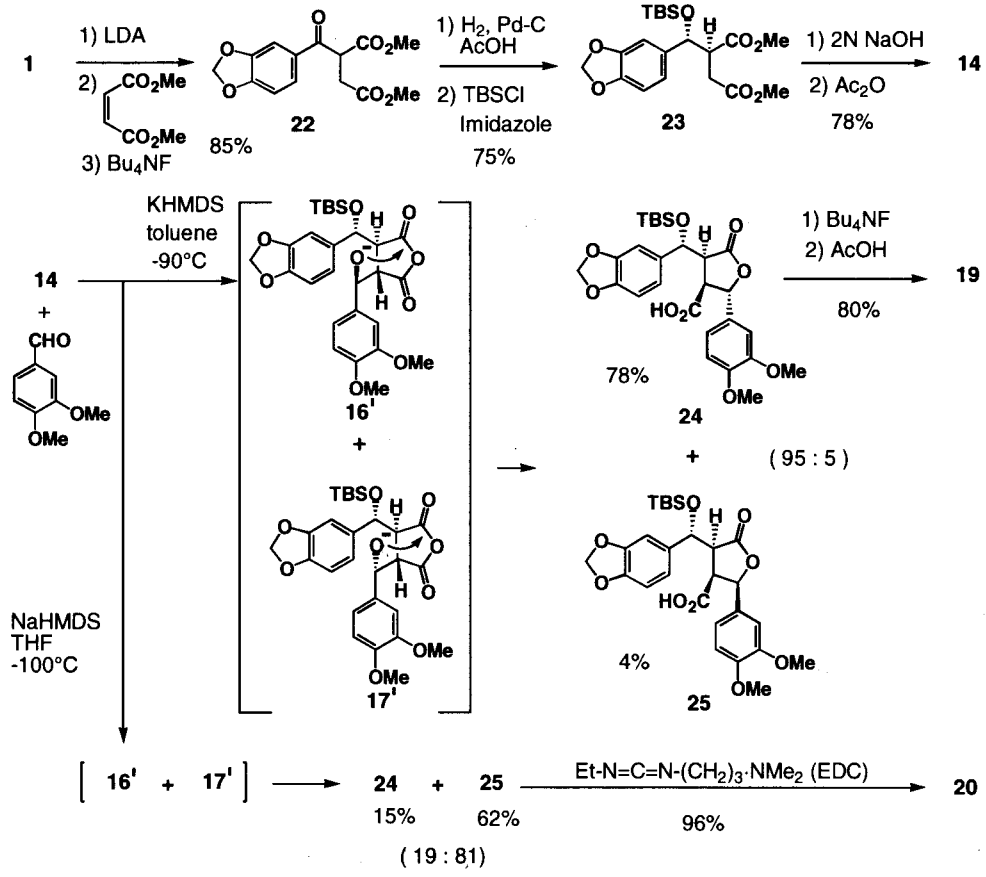


Table 1 Aldol reaction of **14** with veratraldehyde.

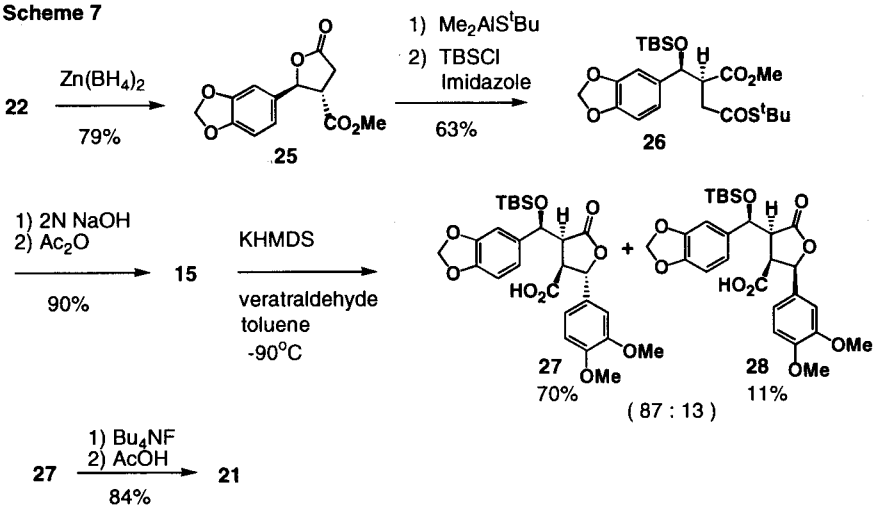
Base	Solvent	Temp. (°C)	Yield (%)	**24** : **25** *
LDA	THF	-50	8	56 : 44
LiHMDS	THF	-50	54	53 : 47
LiHMDS	THF	-100	71	38 : 62
NaHMDS	THF	-50	67	44 : 56
NaHMDS	THF	-100	77	19 : 81
KHMDS	THF	-50	70	92 : 8
KHMDS	Toluene	-50	73	94 : 6
KHMDS	Toluene	-90	82	95 : 5

* Determined by HPLC analysis of the crude reaction products.

As shown in Scheme 6, the authors synthesized the acid anhydride (**14**) stereoselectively in a good overall yield from the cyanohydrin (**1**). Then, aldol reaction of **14** with veratraldehyde was next examined in order to obtain the key intermediates (**16'** and **17'**) stereoselectively. Although Kuwajima and his co-workers have reported the aldol reaction of succinic anhydride with an aliphatic aldehyde, they have not examined the stereoselectivity of the reaction.[14] The authors examined the stereoselectivity of the aldol reaction of **14** with veratraldehyde under various conditions. The results are summarized in Table 1. When the aldol reaction was carried out at -90 °C in toluene using KHMDS as a base, the lactone (**24**), which was produced *via* **16'**, was obtained with high stereoselectivity (**24**:**25** = 95:5) in good yield. The TBS group was removed from **24** followed by cyclization of the product in acetic acid at room temperature to afford the axial-equatorial isomer (**19**).[10a]

In order to obtain the key intermediate for the synthesis of the diaxial isomer (**20**), the aldol reaction of **14** with veratraldehyde was next examined. The *anti*-isomer (**25**) was obtained stereoselectively (**24**:**25** = 19:81) when the aldol reaction was carried out at -100 °C in THF using NaHMDS as a base. After

Scheme 7



removal of the TBS group from **25**, the obtained alcohol was treated with acetic acid. However, the epimerization reaction at C-1 and C-2 took place under the conditions and the yield of the desired *diaxial*-isomer (**20**) was quite low. In order to prevent the epimerization the cyclization reaction under non-acidic conditions was examined. As a result, the axial-isomer (**20**) was obtained in 96% yield when the reaction was carried out at room temperature in DMF using hydrogen chloride free EDC. Synthesis of the *diaxial*-isomer of furofuran lignans has not been known, and the present synthesis is the first one.[10c] On the other hand, the *syn*-type derivative of succinic acid anhydride (**15**) was prepared to synthesize the diequatorial isomer (**21**). The aldol reaction of **15** with veratraldehyde was carried out in the same manner as that of **14** using KHMDS and **27** was converted into the diequatorial bislactone (**21**) in the same manner as that of **24** (Scheme 7).[10b]

Asymmetric Synthesis

Asymmetric synthesis of lignans has recently been intensively studied and several efficient methods based on the diastereoselective alkylation of the chiral butyrolactones, the diastereoselective Michael addition to the chiral butenolide, the asymmetric Diels-Alder reaction, and arylation of the chiral oxazoline derivatives[15] have been reported. Although some of these methods are highly ingenious, difficult accessibility of the chiral substrate used in these methods might be the defect. As described in the above section, we have developed the novel and efficient methods for the stereocontrolled synthesis of the furofuran lignans (**4** and **7**) utilizing the cyanohydrin intermediates (**2**) and (**5**), respectively. Accordingly, the furofuran lignans (**4** and **7**) would be enantioselectively synthesized if enantioselective synthesis of **2** and **5** can be efficiently achieved.

The authors examined the Michael addition reaction of the cyanohydrin (**1**) to the α,β-unsaturated ester (**29**) which can be easily synthesized from the commercially available (s)-(+)-2,2-dimethyl-1,3-dioxolane-4-methanol. Reaction of **1** with **29** was first carried out at -78 ^{o}C in THF using LDA to afford a mixture of **30** and **31** in 73 % yield. However, the diastereoselectivity was only 10 % de. In order to improve the diastereoselectivity, the reaction was examined under various conditions. As a result, the selectivity

was improved by addition of HMPA. Optimization of the reaction conditions revealed that the best result was obtained at -100 °C by adding two equivalents of HMPA; the diastereoselectivity was 93 % de. It is interesting that the low selectivity was observed either in the absence or presence of HMPA when the *trans*- ester was employed. The high diastereoselectivity described above would be accounted for by the stereocontrol based on the 1,3-allylic strain as follows.

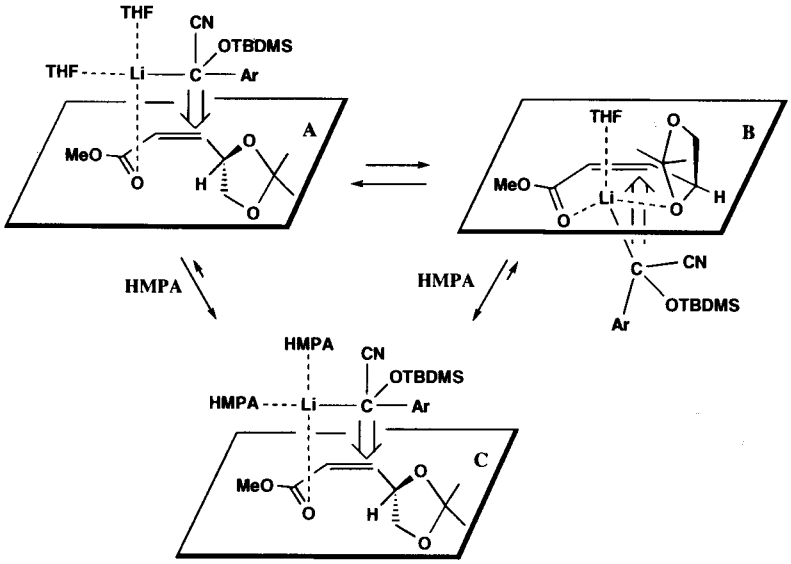


Figure 3

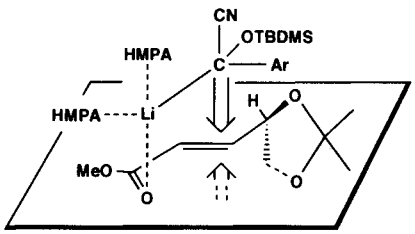


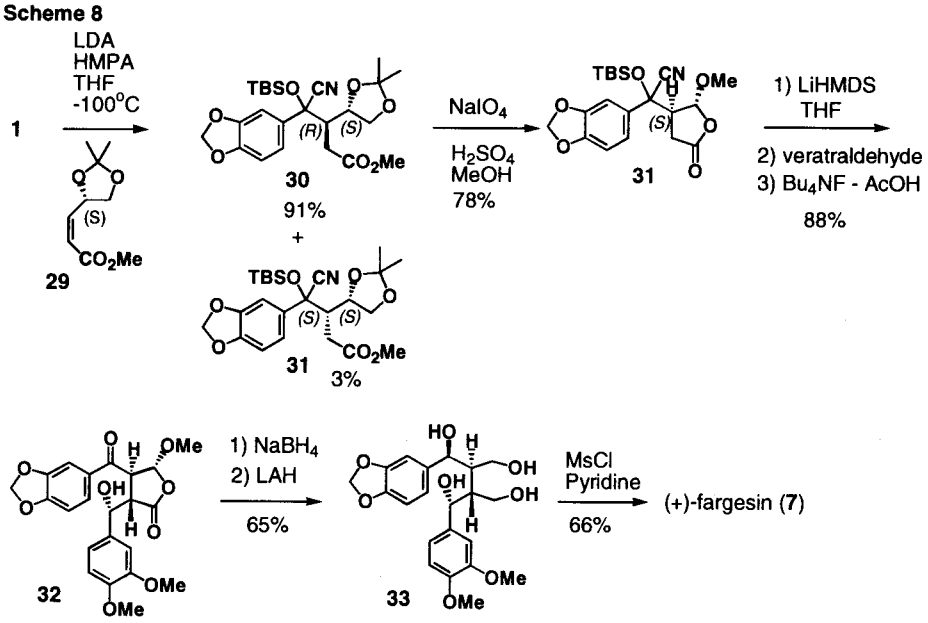
Figure 4

In the reaction of the lithium salt of **1** with the ester (**29**) in the absence of HMPA, the lithium salt would interact with the carbonyl oxygen of **29** and two molecules of THF (Figure 3, A), or interact with the carbonyl oxygen, an oxygen of the 1,3-dioxolane moiety and one molecule of THF (Figure 3, B). In the structure A, the nucleophilic attack would take place predominantly from the sterically less hindered upper face induced by the 1,3-allylic strain. On the other hand, the lithium salt of **1** would attack from the lower face in the structure B. For competition between the mode of reactions, the reaction of **1** with **29** did not proceed in a highly diastereoselective manner. Addition of HMPA would release the lithium cation from the interaction with the 1,3-dioxolane moiety of **29** and promote the attack from the upper face (Figure 3,C). Moreover, the coordinated HMPA would also contribute to enhancement of the diastereoselectivity by making the lithium salt bulkier, where two equivalents of HMPA are required to substitute for the coordinated THF. This would well elucidate that the high diastereoselectivity was observed in the presence of two equivalents of HMPA.

In case of the *trans*-ester (**29'**), the distance between the carbonyl group and the 1,3-dioxolane moiety is longer than that of **29**, and both the stereoselectivity based on 1,3-allylic strain (Figure 4) and the coordination control would not work efficiently either in the absence or in the presence of HMPA. This might be the good reason for the poor diastereoselectivity in case of **29'**.

On the bases of this diastereoselective synthesis, asymmetric synthesis of (+)-fargesin (**7**) was achieved.[16] In order to improve the diastereoselectivity of the aldol reaction of **30**, **30** was converted into the γ-lactone (**31**). As described in the synthesis of **4** and **7**, the *syn*- and *anti*-selectivity in aldol reaction using LiHMDS was not observed in case of the analog of **31** having no substituent on C-5. However, the aldol reaction in the case of **31** proceeded completely in *anti*-selective manner under the same reaction conditions. Conversion of the cyanohydrin part of the aldol adduct into a carbonyl group gave **32** selectively. The carbonyl group of **32** was first reduced stereoselectively with $NaBH_4$ and the ester group was next reduced with $LiAlH_4$ to give **33** selectively. The tetraol (**33**) was cyclized to furnish (+)-fargesin (**7**). Thus, asymmetric syntheses of (+)-fargesin was achieved as a representative example. The present method should be applicable for the asymmetric synthesis of various types of furofuran lignans.

Scheme 8



Conclusion

As described above, stereocontrolled synthesis of furofuran lignans could be achieved by the three component joining reaction consisted of a cyanohydrin, an α,β-unsaturated ester and an aromatic aldehyde, and the aldol reaction of a cinnamic anhydride derivative and an aromatic aldehyde. Asymmetric synthesis of furofuran lignans was also achieved based on the asymmetric Michael addition reaction of a cyanohydrin derivative to the chiral butenolide.

In the synthetic study aiming at development of the new entities of drugs, it is frequently required to synthesize a series of compounds. Because a number of furofuran lignans have been reported to show the intriguing biological activities and have a variety of chemical structures, furofuran lignans should occupy the important position as lead compounds of the research for new drugs. We hope that the present method will be applied to such studies.

The authors would like to acknowledge to the co-workers who participate intensively in the present study.

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