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Asymmetric Syntheses of Lignans Utilizing Novel Diastereoselective Michael Addition of Cyanohydrin: Syntheses of (+)-Fargesin and (-)-Picropodophyllone

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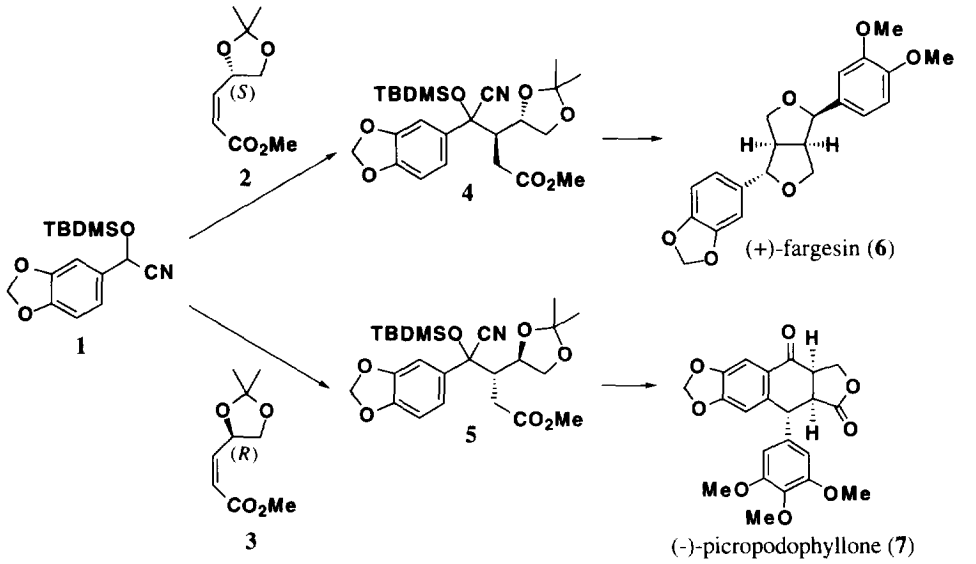
Abstract: The Michael addition reaction of lithium salt of cyanohydrin to (*S*)- and (*R*)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-*cis*-2-propenoate (**2** and **3**) proceeded in 93% de in the presence of two equivalents of HMPA at -100 °C. This diastereoselectivity could be elucidated by the stereocontrol based on the 1,3-allylic strain. Utilizing this reaction, stereocontrolled syntheses of (+)-fargesin (**6**) and (-)-picropodophyllone (**7**) were achieved. © 1997 Elsevier Science Ltd.

INTRODUCTION

Lignans are of increasing interest due to the intriguing biological activities exhibited by some members of this class.[1] Much effort has been devoted to developing efficient methods for the synthesis of lignans.[2] Asymmetric syntheses of lignans have recently been intensively studied, and reported several efficient methods[3] involving those based on the diastereoselective alkylation of the chiral butyrolactones,[4] the diastereoselective Michael addition to the chiral butenolide,[5] the asymmetric Diels-Alder reaction,[6] and arylation of the chiral oxazoline derivatives.[7] Although some of these methods are highly ingenious, rather difficult accessibility of the chiral substrate used in those methods might be the defect.

In connection with our efforts in search of new compounds having intriguing biological activities from lignans, we have developed the novel stereoselective syntheses of lignans utilizing cyanohydrins.[8] In these syntheses, the common key-intermediate was synthesized based on the Michael addition-aldol reaction of an *O-tert*-butyldimethylcyanohydrin, butenolide and an aromatic aldehyde. As an extension of our new syntheses of lignans, we would like to report in this paper a novel highly enantioselective Michael addition of the cyanohydrin **1** to (*S*)- and (*R*)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-*cis*-2-propenoate (**2** and **3**) and its application to the asymmetric syntheses of lignans adopting (+)-fargesin (**6**) and (-)-picropodophyllone (**7**) as representative examples (Scheme 1).[9]

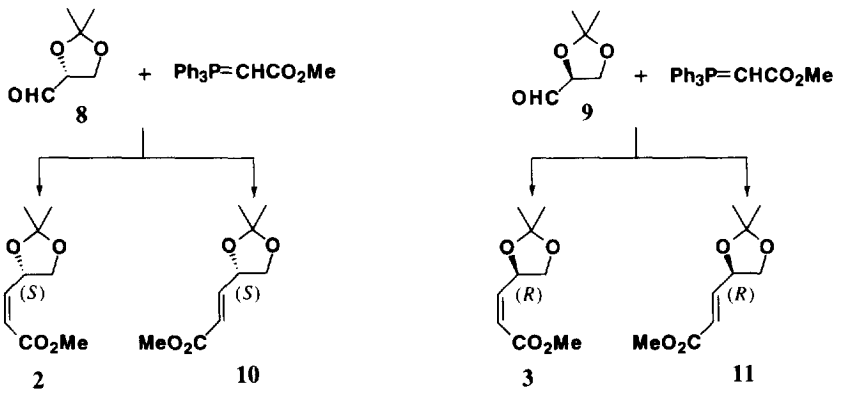


Scheme 1

RESULTS AND DISCUSSION

Diastereoselective Michael Addition of the Cyanohydrin to the α,β-Unsaturated Ester

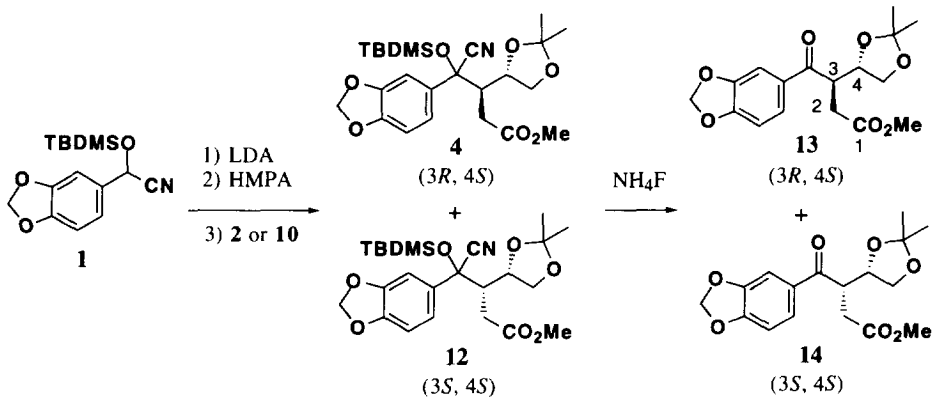
We considered that the chiral α,β-unsaturated ester should be easily accessible in order to develop a practical method, and selected the esters **2**, **3**, **10** and **11** which can be easily prepared from chiral aldehydes **8** and **9** (Scheme 2).[10, 11]



Scheme 2

In order to clarify the feature of the diastereoselectivity of the Michael addition of the cyanohydrin to the ester **2**, **3**, **10** and **11**, the reaction of **1** and **2** was first examined. The Michael addition reaction was first carried out employing lithium diisopropylamide (LDA) in THF at -78 °C, and a mixture of the inseparable Michael adducts **4** and **12** were obtained in 73% yield (Table 1, run 1). Both **4** and **12** consist of the two

isomers derived from stereochemistry at the benzylic position. To examine the ratio of **4** to **12**, the mixture of **4** and **12** was converted into the ketones **13** and **14** by treatment with NH_4F in THF-DMF-H_2O.[12] The stereochemistry of **14** was unambiguously determined by X-ray crystallographic analysis[13] and **13** was determined to be the isomer of **14** at C-3 by ^1H NMR analysis. The diastereoselectivity was, however, revealed to be only 10% de; the yield of **13** and **14** from **1** were 40% and 33%, respectively.



Scheme 3

In order to obtain high diastereoselectivity, the reaction was examined under various conditions, and the diastereoselectivity was found to be remarkably improved by addition of hexamethylphosphoramide (HMPA) to the reaction mixture after lithiation of cyanohydrin **1**.[14] When an equimolar amount of HMPA was used, the Michael adduct was obtained in 88% yield with 74% de (run 2). Furthermore, both the yield and the diastereoselectivity heightened 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 adding two or three equivalents of HMPA (runs 4 and 5). The diastereoselectivity was improved to be 93%, whereas the yield lowered slightly with increasing the amount of HMPA. Thus, the best result was obtained when the reaction was carried out at -100 °C by using two equivalents of HMPA (run 4).

Table 1 Diastereoselectivity of Michael addition of the cyanohydrin **1** to the α,β-unsaturated ester **2** or **10**

Run	Ester	Temp. (°C)	HMPA (eq.)	Yield (**4**+**12**) (%)	De (**13**)[a] (%)
1	**2**	-78	0	73	10
2		-78	1	88	74
3		-100	1	97	80
4		-100	2	94	93
5		-100	3	92	93
6	**10**	-100	0	75	16
7		-100	2	92	22

[a] Determined by HPLC analyses of the crude mixture of **13** and **14**.

On the other hand, low selectivity was observed either in the absence or in the presence of HMPA when the *trans* ester **10** was employed (runs 6 and 7).

Discussion on the Diastereoselectivity

The high diastereoselectivity observed above would be elucidated by the stereocontrol based on the 1,3-allylic strain as followings.[15, 16]

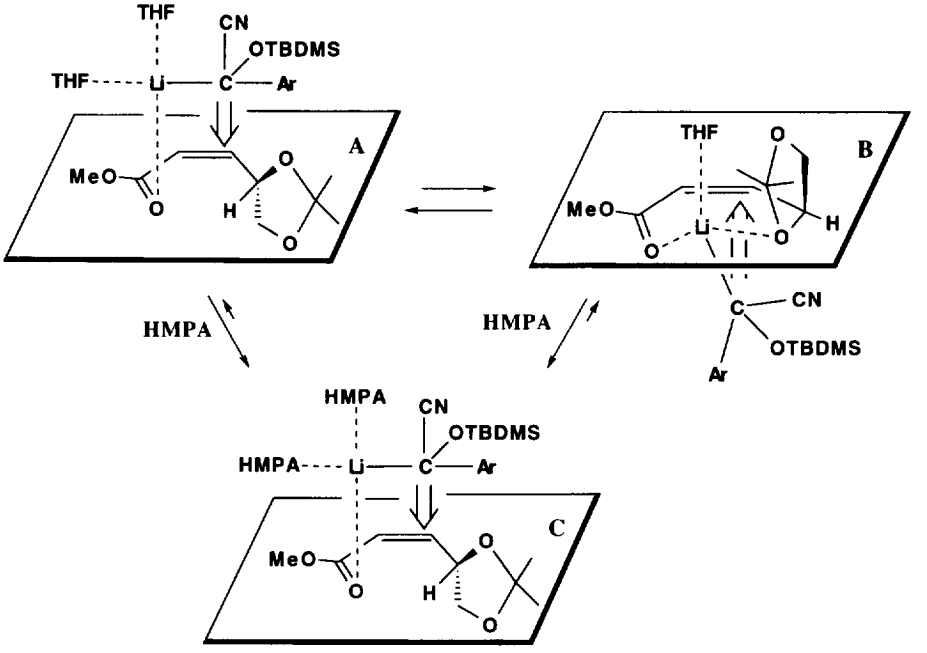


Fig. 1

In the reaction of the lithium salt of **1** with the ester **2** in the absence of HMPA, the lithium salt would interact with the carbonyl oxygen of **2** and two molecules of THF (Fig. 1, **A**), or interact with the carbonyl oxygen, an oxygen of the 1,3-dioxolane moiety and one molecule of THF (Fig. 1, **B**).[17] 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, in the structure **B**, the lithium salt of **1** would attack from the lower face. For the competition between the two mode of reactions, the reaction of **1** with **2** did not proceed in a highly diastereoselective manner. Addition of HMPA would release the lithium cation from the coordination with the 1,3-dioxolane moiety of **2** and promote the attack from the upper face (Fig. 1, **C**). Moreover, the coordinated HMPA would also contribute to the enhancement of the diastereoselectivity by giving the lithium salt additional bulkiness, and two equivalents of HMPA might be required in order to saturate the coordination sites of the lithium salt. This would well elucidate the high diastereoselectivity observed in the presence of two equivalents of HMPA; this would also well elucidate that addition of one equivalent of HMPA was not enough to give the best result and three equivalents of HMPA did not improve the diastereoselectivity.

In the case of the *trans*-ester **10**, the distance between the carbonyl group and the 1,3-dioxolane moiety is longer than that of **2**, and both the stereoselectivity based on 1,3-allylic strain (Fig. 2) and the coordination control would not work efficiently either in the absence or in the presence of HMPA. This might be the reason of the poor diastereoselectivity in case of **10**.[18]

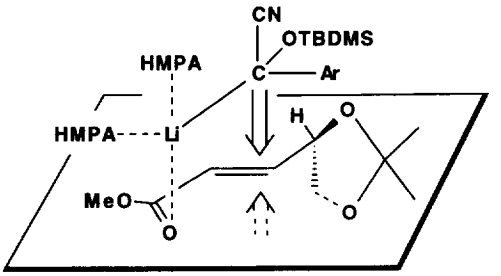


Fig. 2

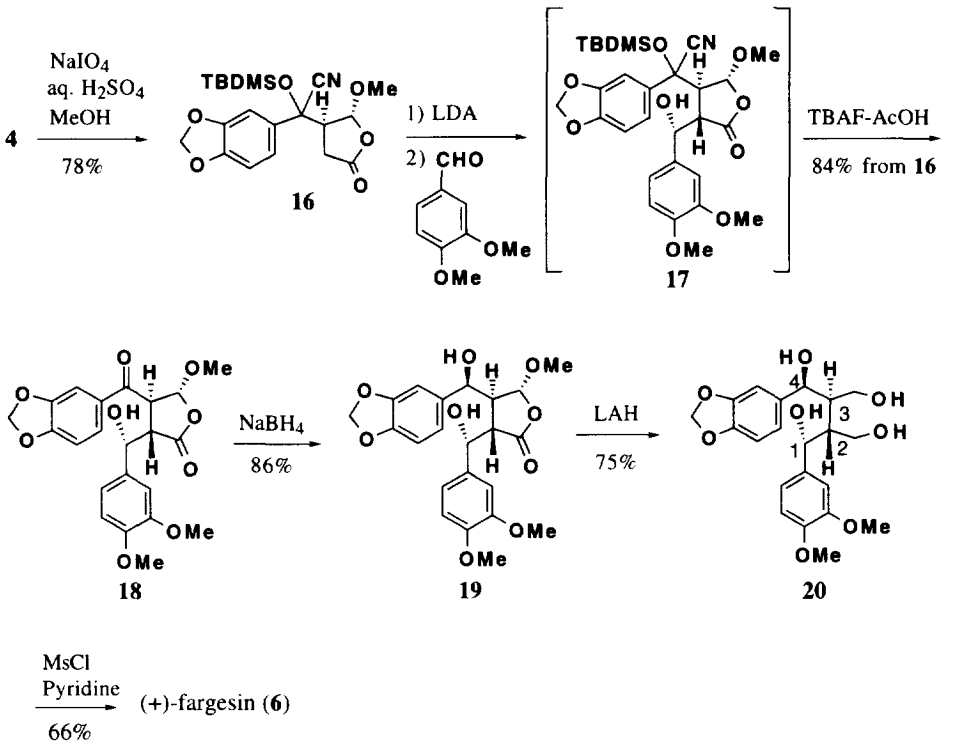
Asymmetric Synthesis of (+)-Fargesin

The discovery of the highly diastereoselective Michael addition reaction of the cyanohydrin **1** to the ester **2** prompted us to apply this reaction to the asymmetric synthesis of (+)-fargesin (**6**).

The Michael adduct **4** obtained above was first converted into the γ-lactone **16** in 78% yield by treatment with sodium metaperiodate in methanol (Scheme 4).[19]

The aldol reaction of **16** with veratraldehyde was next examined. The aldol reaction was carried out in THF at -78 ℃ by using LDA as a base. The adduct **17** was treated with tetrabutylammonium fluoride (TBAF) in dichloromethane containing acetic acid to afford **18** in 84% yield as a sole product. The result obtained in the above reaction was in marked contrast to that observed in the aldol reaction in the syntheses of the racemic furofuran lignans, in which *syn*- and *anti*-isomers were obtained in the ratio of 1:1.[8g] The presence of the methoxyl group of **16** presumably plays an important role to stabilize the chair-transition structure leading to the *anti*-isomer **17**.

Conversion of **18** into (+)-fargesin was then examined. The *anti*-isomer **18** was first reduced with lithium aluminum hydride (LAH). However, no selectivity was observed at C-4 carbon center. This problem was resolved by a stepwise reduction. The ketone **18** was first reduced with sodium borohydride in methanol at 0 ℃ to afford the diol **19** and its C-4 stereoisomer in 86 and 8% yield, respectively. Then, **19** was further reduced with LAH in THF to give the tetraol **20** in 75% yield. Finally, **20** was converted into (+)-fargesin (**6**) in 66% yield by the method previously reported.[8g, 20]



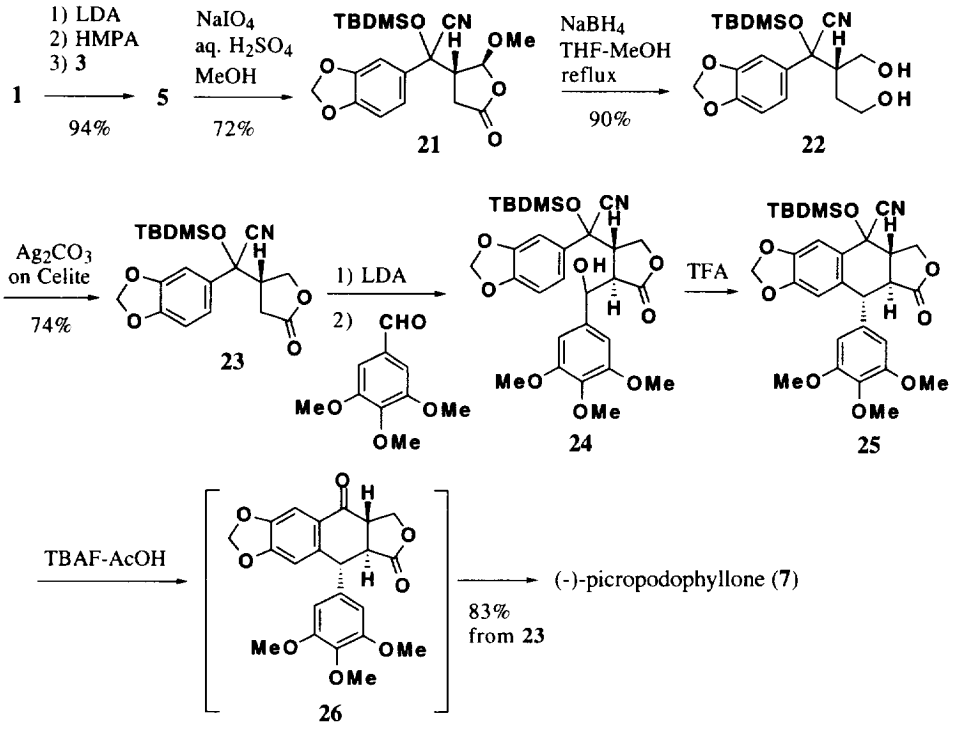
Scheme 4

Asymmetric Synthesis of (-)-Picropodophyllone

The highly diastereoselective Michael addition reaction was also applied to synthesis of (-)-picropodophyllone (**7**), an important precursor in the synthesis of (-)-podopyllotoxin[21] which has been well known as a lignan having intriguing antitumor activity.[22] Because we already reported synthesis of racemic picropodopyllone *via* γ-lactone **23**,[8c] we first examined enantioselective synthesis of **23** (Scheme 5).

The Michael addition reaction of **1** to **3** proceeded in a highly diastereoselective manner under the same reaction conditions described above to afford **5** in 94% yield with 93% de. The Michael adduct **5** was then treated with sodium metaperiodate in methanol to give the γ-lactone **21** in 72% yield in the same method described in the synthesis of **16**. Reduction of **21** with sodium borohydride in hot THF-methanol[23] followed by selective oxidation of the resulting diol **22** with Fétizon's reagent[24] afforded the γ-lactone **23** in 67% yield.[25] The stereochemistry of the chiral carbon centers of **21** was completely reserved during these transformations.[26]

The aldol reaction of **23** and 3,4,5-trimethoxybenzaldehyde was carried out in THF at -78 ℃ using LDA. The product **24** was treated with trifluoroacetic acid (TFA) in dichloromethane at room temperature to afford the cyclized compound **25**. Without purification of the product, **25** was treated with TBAF in dichloromethane containing acetic acid gave (-)-picropodophyllone (**7**) (93% ee) in 83% yield *via* the isomerization of the intermediately generated **26**. Optically pure **7** was obtained by recrystallization from MeOH.



Scheme 5

CONCLUSION

As described above, we found that the Michael addition reaction of the cyanohydrin **1** to the chiral α,β-unsaturated esters **2** and **3** proceeded in a highly diastereoselective manner in the presence of two molar equivalents of HMPA. The diastereoselectivity would be elucidated by the stereocontrol based on the 1,3-allylic strain. The diastereoselective Michael addition reaction has been recently studied intensively and several highly diastereoselective ones have been developed. The present method might be one of the most effective one, and should provide a powerful method in asymmetric synthesis of the naturally occurring compounds involving the lignans synthesized in the present work.

EXPERIMENTAL SECTION

Melting points were measured on a Büchi 535 capillary melting point apparatus and are uncorrected. Elemental analyses were performed on a Perkin-Elmer 2400II. IR spectra were recorded on a Perkin-Elmer 1640 spectrophotometer. ^{1}H NMR spectra (200 MHz) and ^{13}C NMR spectra (50 MHz) were obtained on a Bulker AC-200 spectrometer in $CDCl_3$ with TMS as an internal standard. Mass spectra were recorded on a Hitachi M-2000A or JMS-HX100. Analytical HPLC was carried out on a Shimadzu LC-6A using SHISEIDO CAPCELLPAC C18 column with CH_3CN-H_2O solvent system, or DAICEL CHIRALCEL OJ column with

hexane-2-propanol solvent system. Column chromatography was carried out on silica gel (Kieselgel 60, 230-400 mesh, E. Merk).

Methyl (3*R*, 4*S*)-4,5-*O*-Isopropylidene-3-(3,4-methylenedioxybenzoyl)-4,5-dihydroxypentanoate (13) and **Methyl (3*S*, 4*S*)-4,5-*O*-Isopropylidene-3-(3,4-methylenedioxybenzoyl)-4,5-dihydroxypentanoate (14)**. To the solution of LDA (3.8 mmol) in THF (20 mL) was added dropwise the cyanohydrin **1** (1.0 g, 3.4 mmol) in THF (2 mL) at -78 ℃ under nitrogen atmosphere, and the reaction mixture was stirred at the same temperature for 10 min. To the mixture was added HMPA (1.2 mL, 6.8 mmol) in THF (2 mL) and **2**[10a] (640 mg, 3.4 mmol) in THF (2 mL) was added at -100 ℃. After 30 min, the mixture was quenched by addition of saturated aqueous NH_4Cl (10 mL) and diluted with AcOEt (50 mL). The organic layer was separated and the aqueous layer was extracted with AcOEt (50 mL). The combined organic extracts were washed with brine (50 mL) and dried over anhydrous magnesium sulfate. After evaporation of the solvent, the residue was chromatographed on silica gel using hexane/AcOEt (4:1) as an eluent to afford an inseparable mixture of **4** and **12** (1.54 g, 94%). To a solution of the mixture in THF/DMF/H_2O (10:2.5:1, 30 mL) was added NH_4F (378 mg, 10 mmol), and the resulting mixture was stirred at room temperature for 6 h. The mixture was diluted with AcOEt (100 mL), washed with water (100 mL) and brine (100 mL), and dried over anhydrous magnesium sulfate. The solvent was evaporated to dryness *in vacuo* to afford a mixture of **13** and **14**. The ratio of **13** to **14** was determined to be 96.4 : 3.6 by HPLC. The mixture was purified by silica gel chromatography using hexane/AcOEt (20:1) as an eluent to afford **13** (1.05 g, 91% from **1**) and **14** (23 mg, 2% from **1**).

13: $[\alpha]_D^{25}$ -42.5° (*c* 1.0, $CHCl_3$); IR (film) 1736, 1672 cm^{-1}; ^1H NMR δ 1.28 (s, 3H), 1.40 (s, 3H), 2.53 (dd, 1H, *J* = 4.1, 16.8 Hz), 2.96 (dd, 1H, *J* = 9.5, 16.8 Hz), 3.62 (s, 3H), 3.78 (dd, 1H, *J* = 6.5, 8.6 Hz), 3.96 (dd, 1H, *J* = 6.5, 8.6 Hz), 4.18 (m, 1H), 4.34 (dd, 1H, *J* = 6.5, 13.0 Hz), 6.05 (2H, s), 6.88 (d, 1H, *J* = 8.2 Hz), 7.49 (d, 1H, *J* = 1.7 Hz), 7.68 (dd, 1H, *J* = 1.7, 8.2 Hz); HRMS (FAB) *m/z* calcd for $C_{17}H_{20}O_7$ + H 337.1287 (M^+ + H), found 337.1292.

14: mp 94-95 ℃; $[\alpha]_D^{25}$ +74.1° (*c* 1.0, $CHCl_3$); IR (KBr) 1719, 1664 cm^{-1}; ^1H NMR δ 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, 8.6 Hz), 3.96 (m, 2H), 4.25 (m, 1H), 6.06 (2H, s), 6.88 (d, 1H, *J*=8.2 Hz), 7.48 (d, 1H, *J* = 1.7 Hz), 7.66(dd, 1H, *J*=1.7, 8.2 Hz); MS (EI) *m/z* 336 (M^+). Anal. Calcd for $C_{17}H_{20}O_7$: C, 60.71; H, 5.99. Found: C, 60.66; H, 5.97.

(3*R*)-[α(*R*)-*tert*-Butyldimethylsilyloxy-α-cyano-3,4-methylenedioxybenzyl]-(4*R*)-methoxybutyrolactone (16a) and **(3*R*)-[α(*S*)-*tert*-Butyldimethylsilyloxy-α-cyano-3,4-methylenedioxybenzyl]-(4*R*)-methoxybutyrolactone (16b)**. Sodium metaperiodate (1.4 g, 6.9 mmol) in 1N sulfuric acid (30 mL) was added to a solution of a mixture of **4** and **12** (820 mg, 1.72 mmol, **4** : **12** = 96.4 : 3.6) in methanol (40 mL) at 40 ℃ and the mixture was stirred at the same temperature for one day. After methanol was evaporated under reduced pressure, the mixture was diluted with AcOEt (100 mL) and washed with brine (60 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was chromatographed on silica gel using hexane/chloroform/AcOEt (20:20:1) as an eluent to afford **16a** (370 mg, 53 %) and **16b** (171 mg, 25 %).

16a: mp 138-139 °C; $[\alpha]_D^{26}$ -1.8° (*c* 1.0, $CHCl_3$): IR (KBr) 1786 cm^{-1}; ^1H NMR δ -0.10 (s, 3H), 0.22 (s, 3H), 0.90 (s, 9H) 2.38 (dd, 1H, *J* = 4.2, 18.2 Hz), 2.65 (dd, 1H, *J* = 9.7, 18.2 Hz), 2.80 (m, 1H), 3.38 (s, 3H) 5.34 (d, 1H, *J* = 2.0 Hz), 5.99 (s, 2H), 6.78 (d, 1H, *J* = 8.2 Hz), 7.49 (d, 1H, *J* = 1.9 Hz), 7.04 (dd, 1H, *J* = 1.9, 8.2 Hz); MS (EI) *m/z* 405 (M^+). Anal. Calcd for $C_{20}H_{27}NO_6Si$: C, 59.24; H, 6.71; N, 3.45. Found: C, 59.20; H, 6.71; N, 3.40.

16b: $[\alpha]_D^{26}$ -24.3°(*c* 1.0, $CHCl_3$); IR (KBr) 1783 cm^{-1}; ^1H NMR δ 0.02 (s, 3H), 0.29 (s, 3H), 0.95 (s, 9H), 2.55 (m, 2H), 2.80 (m, 1H), 3.48 (s, 3H), 5.39 (d, 1H, *J* = 2.0 Hz), 6.03 (s, 2H), 6.70 (d, 1H, *J* = 8.4 Hz), 7.45 (d, 1H, *J* = 1.9 Hz), 7.10 (dd, 1H, *J* = 1.9, 8.4 Hz); HRMS (FAB) *m/z* calcd for $C_{20}H_{27}NO_6Si$ + Na 428.1505 (M^+ + Na), found 428.1506.

(2*S*)-[α(*R*)-Hydroxy-3,4-dimethoxybenzyl]-(3*R*)-(3,4-methylenedioxybenzoyl)-(4*R*)-methoxybutyrolactone (18). To the solution of LDA (11 mmol) in THF (80 mL) was added dropwise **16** (4.3 g, 10 mmol, **16a** : **16b** = 2 : 1) in THF (30 mL) at -78 °C under nitrogen atmosphere and the reaction mixture was stirred at the same temperature for 10 min. To the mixture was added veratraldehyde (1.8g, 11 mmol) in THF (20 mL) at the same temperature. After 30 min the mixture was quenched by addition of saturated aqueous NH_4Cl (20 mL). The organic layer was separated and the aqueous layer was extracted with AcOEt (200 mL). The combined organic extracts were washed with brine (100 mL) and dried over anhydrous magnesium sulfate. After evaporation of the solvent, the obtained residue was dissolved in dichloromethane (100 mL) and added TBAF (1M, in THF, 20 mL, 20 mmol) containing acetic acid (1.3 mL, 22 mmol) at room temperature. After 2 h the solution was washed with water (50 mL), 10% citric acid (50 mL), brine (50 mL) and dried over anhydrous magnesium sulfate. After evaporation of the solvent, the residue was purified by silica gel column chromatography using hexane/AcOEt (3:1) as an eluent to afford **18** (3.6 g, 84%): $[\alpha]_D^{20}$ -42.1° (*c* 1.0, $CHCl_3$); IR (film) 3503, 1769, 1672 cm^{-1}; ^1H NMR ($CDCl_3$ + D_2O) δ 3.53 (s, 3H), 3.60 (dd, 1H, *J* = 8.5, 8.8 Hz), 3.76 (s, 3H), 3.77 (dd, 1H, *J* = 4.6, 8.5 Hz), 3.78 (s, 3H), 4.88 (d, 1H, *J* = 8.8 Hz), 5.30 (d, 1H, *J* = 4.6 Hz), 6.03 (s, 2H), 6.58 (d, 1H, *J* = 9.2 Hz), 6.69-6.81(m, 3H), 7.02 (d, 1H, *J* = 1.8 Hz), 7.15 (dd, 1H, *J* = 1.8, 8.2 Hz); HRMS (FAB) *m/z* calcd for $C_{22}H_{22}O_9$ + Na 453.1162 (M^+ + Na), found 453.1150.

(2*S*)-[α(*R*)-Hydroxy-3,4-dimethoxybenzyl]-(3*S*)-[α(*S*)-hydroxy-α-3,4-methylenedioxybenzyl]-(4*R*)-methoxybutyrolactone (19) and **(2*S*)-[α(*R*)-Hydroxy-3,4-dimethoxybenzyl]-(3*S*)-[α(*R*)-hydroxy-3,4-methylenedioxybenzyl]-(4*R*)-methoxy-butyrolactone (isomer of 19).** To a solution of **18** (3.8 g, 8.8 mmol) in methanol (30 mL) was added $NaBH_4$ (330 mg, 8.8 mmol) at 0 °C and the mixture was stirred at the same temperature for 30 min. The reaction mixture was quenched by addition of water (1 mL) and diluted with AcOEt (300 mL). The organic layer was washed with brine (10 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was chromatographed on silica gel using hexane/chloroform/AcOEt (5:5:1) as an eluent to afford **19** (3.2g, 86%) and its isomer (302 mg, 8%).

19: mp 139 °C; $[\alpha]_D^{20}$ -84.4° (*c* 1.0, $CHCl_3$); IR (KBr) 3419, 1758 cm^{-1}; ^1H NMR ($CDCl_3$ + D_2O) δ 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); MS (EI) *m/z* 432 (M^+). Anal. Calcd for $C_{22}H_{24}O_9$: C, 61.11; H, 5.59. Found: C, 60.96; H, 5.56.

Isomer of **19**: mp 120 °C; $[\alpha]_D^{20}$ -18.0° (*c* 1.0, $CHCl_3$); IR (KBr) 3440, 1751 cm^{-1}; ^1H NMR ($CDCl_3$ + D_2O) δ 2.28 (m, 1H), 2.48 (dd, 1H, *J* = 3.6, 9.7 Hz), 3.50 (s, 3H), 3.72 (s, 3H), 3.88 (s, 3H), 4.06 (d, 1H, *J* = 8.6 Hz), 4.77 (d, 1H, *J* = 9.7 Hz), 5.53 (d, 1H, *J* = 1.6 Hz), 5.94 (d, 1H, *J*=1.6 Hz), 6.02 (d, 1H, *J* = 1.6 Hz), 6.18 (d, 1H, *J* = 1.6 Hz), 6.42 (dd, 1H, *J* = 1.6, 7.9 Hz), 6.57-6.77 (m, 4H); MS (EI) *m/z* 432 (M^+). Anal. Calcd for $C_{22}H_{24}O_9$: C, 61.11; H, 5.59. Found: C, 60.87; H, 5.48.

(1*R*, 2*R*, 3*R*, 4*S*)-2,3-Bis(hydroxymethyl)-1-(3,4-dimethoxyphenyl)-4-(3,4-methylenedioxyphenyl)butane-1,4-diol (20). To a suspension of LAH (1.58 g, 42 mmol) in THF (100 mL) was added **19** (1.8 g, 4.2 mmol) in THF (20 mL) at 60 °C and the mixture was stirred at the same temperature for 1 h. The mixture was quenched by addition of 10% sodium hydroxide (4 mL) at 0 °C and the mixture was stirred at the room temperature for 6 h. The insoluble materials were filtered off by a Celite pad. The filtrate was evaporated to dryness *in vacuo*. The residue was purified by silica gel chromatography using chloroform/MeOH (20:1) as an eluent to afford **20** (1.28 g, 75%): mp 126-127 °C; $[\alpha]_D^{20}$ -39.0° (*c* 0.20, $CHCl_3$); IR (KBr) 3314 cm^{-1}; ^1H NMR ($CDCl_3$ + D_2O) δ 1.97 (m, 1H), 2.05 (m, 1H), 3.79 (s, 3H), 3.87 (s, 3H), 3.9-4.1 (m, 4H), 4.73 (d, 1H, *J* = 6.4 Hz), 4.97 (d, 1H, *J* = 5.0 Hz), 5.95 (s, 2H), 6.57 (d, 1H, *J* = 1.7 Hz), 6.7-6.9 (m, 5H); MS (EI) *m/z* 406 (M^+). Anal. Calcd for $C_{21}H_{26}O_8$: C, 62.06; H, 6.45. Found: C, 61.76; H, 6.31.

(+)-Fargesin (6). To a stirred solution of **20** (950 mg, 2.34 mmol) in dichloromethane (19 mL) containing pyridine (1.9 mL) was added dropwise MsCl (0.543 mL, 7.01 mmol) at 0 °C. The mixture was stirred at 0 °C for 6 h and at room temperature for 10 h. The mixture was washed with water (50 mL), 10% citric acid (50 mL), and brine (50 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was purified by silica gel chromatography using hexane/AcOEt (4:1) as an eluent to afford **6** (571 mg, 66%): mp 135-136 °C; $[\alpha]_D^{20}$ +122° (*c* 1.0, $CHCl_3$); IR (KBr) 2874, 1591, 1517, 1231, 1028 cm^{-1}; ^1H NMR δ 2.87 (m, 1H), 3.2-3.4 (m, 2H), 3.8-3.9 (m, 2H), 3.88, (s, 3H), 3.91 (s, 3H), 4.12 (br d, 1H, *J* = 9.3 Hz), 4.42 (d, 1H, *J* = 7.0 Hz), 4.87 (d, 1H, *J* = 5.3 Hz), 5.95 (s, 2H), 6.7-6.9 (m, 6H); ^{13}C NMR δ 50.25, 54.68, 55.99, 69.78, 71.12, 82.12, 87.73, 101.06, 106.59, 108.19, 109.29, 111.32, 117.85, 119.54, 131.12, 135.36, 147.26, 148.03, 148.23, 149.06; MS (EI) *m/z* 370 (M^+). Anal. Calcd for $C_{21}H_{22}O_6$: C, 68.10; H, 5.99. Found: C, 67.97; H, 5.92.

(2*S*)-[α(*S*)-*tert*-Butyldimethylsilyloxy-α-cyano-3,4-methylenedioxybenzyl]butane-1,4-diol (22a) and **(2*S*)-[α(*R*)-*tert*-Butyldimethylsilyloxy-α-cyano-3,4-methylenedioxybenzyl]-butane-1,4-diol (22b)**. The γ-Lactone **21a** (the enantiomer of **16a**) and **22b** (the enantiomer of **16b**) was obtained in 49% and 23% from **1** and **3** in the same method described in the synthesis of **16a** and **16b**. To a solution of **21a** (350 mg, 0.863 mmol) in THF (10 mL) was added $NaBH_4$ (164 mg, 4.3 mmol). The mixture was heated under reflux and methanol (1 mL) was added dropwise over 30 min and the reaction mixture was

refluxed for another 30 min. The reaction mixture was diluted with AcOEt (50 mL) and washed with brine (30 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was chromatographed on silica gel using hexane/AcOEt (1:1) as an eluent to afford **22a** (295 mg, 90%). **22b** was obtained from **21b** in 90% yield in the same manner described above.

22a: $[\alpha]_D^{25}$ -40.7° (*c* 1.4, $CHCl_3$); IR (film) 3484 cm^{-1}; ^1H NMR ($CDCl_3$ + D_2O) δ -0.13 (s, 6H), 0.94 (s, 9H), 1.58 (m, 2H), 2.27 (m, 1H), 3.48-3.85 (m, 3H), 4.09 (m, 1H), 6.04 (s, 2H), 6.82 (d, 1H, *J* = 8.2 Hz), 7.00 (d, 1H, *J* = 1.8 Hz), 7.08 (dd, 1H, *J* = 1.8, 8.2 Hz); HRMS (FAB) *m/z* calcd for $C_{19}H_{29}NO_5Si$ + Na 402.1713 (M^+ + Na), found 402.1699.

22b: $[\alpha]_D^{25}$ +33.8° (*c* 0.51, $CHCl_3$); IR (film) 3482 cm^{-1}; ^1H NMR ($CDCl_3$ + D_2O) δ 0.04 (s, 3H), 0.10 (s, 3H), 1.00 (s, 9H), 1.72 (m, 2H), 2.40 (m, 1H), 3.51 (m, 2H), 4.03 (dd, 1H, *J* = 8.4, 10.3 Hz), 4.41 (m, 1H), 5.98 (s, 2H), 6.77-6.90 (m, 3H); HRMS (FAB) *m/z* calcd for $C_{19}H_{29}NO_5Si$ + Na 402.1713 (M^+ + Na), found 402.1714.

(3*S*)-[α(*S*)-*tert*-Butyldimethylsilyloxy-α-cyano-3,4-methylenedioxybenzyl]butyrolactone (23a) and **(3S)-[α(*R*)-*tert*-Butyldimethylsilyloxy-α-cyano-3,4-methylenedioxybenzyl]-butyrolactone (23b)**. To a solution of **22a** (180 mg, 0.474 mmol) in toluene (30 mL) was added silver carbonate (50% on Celite, 2.6 g, 4.7 mmol). The reaction mixture was refluxed overnight. The reaction mixture was filtered and washed with AcOEt. The filtrate and washings were concentrated and the residue was chromatographed on silica gel using hexane/AcOEt (6:1) as an eluent to afford **23a** (132 mg, 74%). **23b** was obtained from **22b** in 73 % yield in the same manner described above.

23a: mp 157-8 °C; $[\alpha]_D^{24}$ -17.6° (*c* 1.0, $CHCl_3$); IR (KBr) 1772 cm^{-1}; ^1H NMR δ -0.03 (s, 3H), 0.24 (s, 3H), 0.95 (s, 9H), 2.44 (dd, 1H, *J* = 9.2, 17.9 Hz), 2.53 (dd, 1H, *J* = 8.3, 17.9 Hz), 3.12 (m, 1H), 4.2-4.5 (m, 2H), 6.04 (s, 2H), 6.83 (d, 1H, *J* = 8.1 Hz), 6.96 (d, 1H, *J* =1.9 Hz), 7.05 (dd, 1H, *J* = 1.9, 8.1 Hz); MS (EI) *m/z* 375 (M^+). Anal. Calcd for $C_{19}H_{25}NO_5Si$: C, 60.78; H, 6.71; N, 3.73. Found: C, 60.56; H, 6.62; N, 3.63.

23b: mp 101 °C; $[\alpha]_D^{24}$ +64.9° (*c* 1.2, $CHCl_3$); IR (film) 1775 cm^{-1}; ^1H NMR δ -0.02 (s, 3H), 0.25 (s, 3H), 0.95 (s, 9H), 2.4-2.8 (m, 2H), 3.08 (m, 1H), 4.2-4.5 (m, 2H), 6.04 (s, 2H), 6.83 (d, 1H, *J* = 8.2 Hz), 6.94-7.07 (m, 2H); MS (EI) *m/z* 375 (M^+). Anal. Calcd for $C_{19}H_{25}NO_5Si$: C, 60.78; H, 6.71; N, 3.73. Found: C, 60.94; H, 6.58; N, 3.66.

(-)-Picropodophyllone (7). A 2:1 isomeric mixture of **23a** and **23b** (**23**) was prepared from a 2:1 isomeric mixture of **21a** and **21b** in the same method described above. To the solution of LDA (1.56 mmol) in THF (20 mL) was added dropwise **23** (531 mg, 1.41 mmol) in THF (5 mL) at -78 °C under nitrogen atmosphere and the reaction mixture was stirred at the same temperature for 10 min. To the mixture was added 3,4,5-trimethoxylbenzaldehyde (305 mg, 1.56 mmol) in THF (3 mL) at the same temperature. The mixture was quenched by addition of saturated aqueous NH_4Cl (5 mL). The organic layer was separated and the aqueous layer was extracted with AcOEt (50 mL). The combined organic extracts were washed with brine (50 mL) and dried over anhydrous magnesium sulfate. After evaporation of the solvent, the residue was dissolved in dichloromethane (3 mL) and TFA (3 mL). After stirring for 8 h at room temperature, the reaction mixture was diluted with dichloromethane (30 mL) and washed with water (30 mL), saturated aqueous $NaHCO_3$ (30 mL), and brine (30 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated *in*

vacuo. The residue was dissolved in dichloromethane (20 mL) and to the mixture was added TBAF (1M in THF, 1.7 mL, 1.7 mmol) containing acetic acid (0.15 mL, 2.6 mmol) at 0 ℃ and the mixture was stirred for 6 h at room temperature. The mixture was washed with 1N hydrochloric acid (20 mL) and brine (20 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using hexane/AcOEt (2:1) as an eluent to afford **7** (484 mg, 83%, 93% ee by HPLC). Recrystallization of a sample of 300 mg of synthetic (-)-picropodophyllone from methanol gave 219 mg of crystalline (-)-**7** (over 99% ee by HPLC): mp 150-151 ℃ (lit.[26] 150 ℃); $[\alpha]_D^{26}$ -140° (*c* 1.0, $CHCl_3$) (lit.[26] 142°); IR (KBr) 1770 cm^{-1}; ^1H NMR δ 3.31 (br s, 2H), 3.75 (s, 6H), 3.80 (s, 3H), 4.32-4.37 (m, 1H), 4.69 (s, 1H), 4.76 (d, 1H, J = 9.2 Hz), 6.05 (s, 2H), 6.24 (s, 2H), 6.69 (s, 1H), 7.50 (s, 1H); ^{13}C NMR δ 43.40, 43.50, 46.70, 56.26, 60.83, 70.49, 102.22, 104.88, 106.06, 109,44, 127.33, 137.53, 138.05, 139.60, 148.49, 153.83, 175.50, 193.46; MS (EI) *m/z* 412 (M^+). Anal. Calcd for $C_{22}H_{20}O_8$: C, 64.07; H, 4.89. Found: C, 63.95; H, 4.81.

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16. The diastereoselective Michael addition reaction of nitromethyl anion and the lithium enolate to the ester **2** have been reported. In the case of nitromethyl anion, the selectivity was elucidated by the stereocontrol based on the 1,3-allylic strain. The present reaction is the first example of the diastereoselective Michael addition of an acyl anion equivalent to **2**: a) Patrocinio, V. L.; Costa, P. R. R.; Correia, C. R. D. *Synthesis* **1994**, 474. b) Nagaoka, H.; Shibuya, K.; Kobayashi, K.; Miura, I.; Muramatu, M.; Yamada, Y. *Tetrahedron Lett.* **1993**, *34*, 4039.
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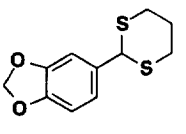
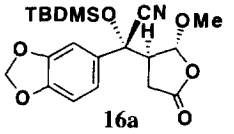
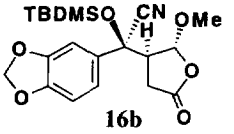
18. The Michael addition of the corresponding dithiane compound to **2** was examined under the similar reaction conditions, however the diastereoselectivity was only 56% de. The rather smaller bulkiness of the 1,3-dithiane compound would brought about the low diastereoselectivity even in the presence of HMPA.



19. γ-Lactone **16** was a mixture of **16a** and **16b** (2:1). The stereochemistry of the major product **16a** was unambiguously determined based on X-ray crystallographic analysis. The stereochemistry of the minor product **16b** was determined as the diastereomer of **16a** on the basis of ^{1}H NMR. The mixture was subjected to the next reaction without separation because both isomers were convertible into (+)-fargesin. Crystal data for **16a** has been deposited at the Cambridge Crystallographic Data Centre.





20. ^{1}H and ^{13}C NMR spectra was identical with (±)-fargesin we have already reported.[8h] The optical purity of synthesized **6** was determined to be over 99% ee by HPLC. Theoretically, obtained **6** was 93% ee, but removal of the enantiomer would be achieved in the crystallization step of tetraol **20**.

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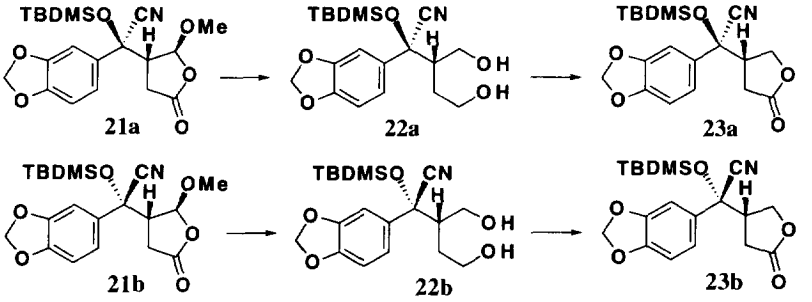
25. Oxidation of diol **22** was proceeded stereoselectively and no stereoisomer was obtained.

26. In order to clarify whether racemization took place or not in the transformation of **21** to **23**, **21a** and **21b** were isolated and independently subjected to the transformation under the same reaction conditions. As a result, **21a** and **21b** were converted into **23a** and **23b** respectively without contamination of the isomer.



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