Simple Synthesis of *trans*-α,β-Dibenzyl-γ-butyrolactone Lignans by Diastereoselective Reduction of α-Benzylidene-β-benzyl-γ-butyrolactones Using $NaBH_4$–$NiCl_2$

Yasunori Moritani, Chiaki Fukushima,† Toshikazu Miyagishima,† Hiroshi Ohmizu,* and Tameo Iwasaki*,††

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

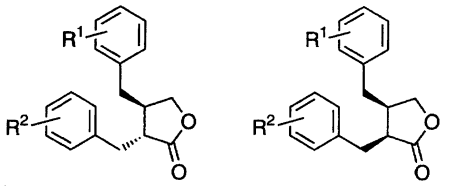
†Tanabe Seiyaku Co., Ltd., 2-2-50 Kawagishi, Toda, Saitama 335

††R&D Planning Division, Tanabe Seiyaku Co., Ltd., 3-16-89 Kashima, Yodogawa, Osaka 532

(Received March 5, 1996)

trans-α,β-Dibenzyl-γ-butyrolactone lignans were synthesized by stereoselective reduction of α-benzylidene-β-benzyl-γ-butyrolactones using $NaBH_4$–$NiCl_2$. The reduction is found to proceed via conjugate addition of a hydride to an α-benzylidene-β-benzyl-γ-butyrolactone and the stereoselective protonation of the resulting metal enolate. The stereoselectivity would be brought about by the conformational rigidity of the phenyl moiety of the α-benzyl group induced by 1,3-allylic strain.

Lignans[1] of the *trans*-α,β-dibenzyl-γ-butyrolactone series **1** have attracted considerable interest because of their intriguing biological activities (Fig. 1).[2] This series of lignans have been synthesized based on the reactions involving benzylation of β-benzyl-γ-butyrolactones,[3] reduction of the dimer of cinnamic acid derivatives[4] and conjugate addition of a benzyl anion to 2-butenolide.[5] Of these methods, benzylation of β-benzyl-γ-butyrolactones seems to be the most concise one considering the easy accessibility of the starting materials and the high stereoselectivity. Indeed, enterolactone **1e**,[2c—2e] isolated from human females, has been efficiently synthesized in a highly enantioselective manner based on this method.[3g] However, the deficiency of this method involves the troublesome handling of the unstable benzyl bromides having multi-oxygen substituents, frequently observed in the naturally occurring lignans, on the benzene ring. In connection with our synthetic studies in search of new compounds having interesting biological activities from lignan derivatives,[6] we wish to report herein a novel method for the synthesis of this series of lignans by the diastereoselective reduction of the α-benzylidene-β-benzyl-γ-butyrolactones **3** based on the diastereoselectivity induced by 1,3-allylic strain.

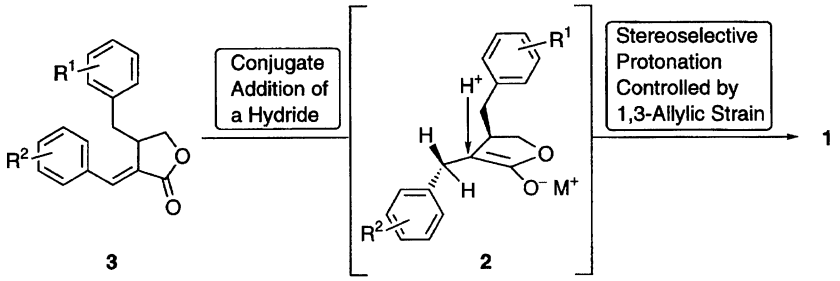


1 **1'**

R^1	R^2
a: 3,4-$(OMe)_2$	3,4-OCH_2O
b: 3,4,5-$(OMe)_3$	3,4-OCH_2O
c: 3,4-$(OMe)_2$	3-OMe,4-OCH_2Ph
d: 3,4,5-$(OMe)_3$	3,4,5-$(OMe)_3$
e: 3-OH	3-OH

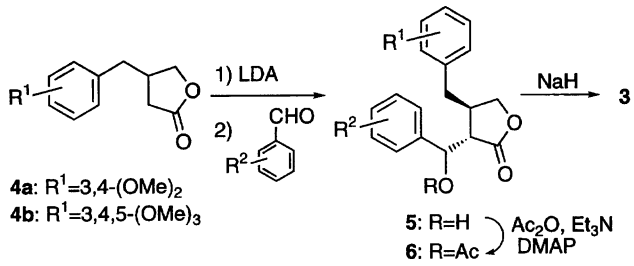
Fig. 1.

We have already reported that the attack of an oxygen electrophile on the metal enolate of α,β-dibenzyl-γ-butyrolactones **1** and **1'** takes place predominantly from the same face as the β-benzyl group due to the shielding effect of the phenyl moiety of the α-benzyl group, which is induced by 1,3-allylic strain.[7] On the basis of this knowledge, we envisaged that the *trans*-α,β-dibenzyl-γ-butyrolactones would be obtained stereoselectively by conjugate addition of a hydride to **3** followed by electrophilic addition of a proton to the resulting enolate **2** (Scheme 1). To estimate the diastereoselectivity in the electrophilic addition of a proton to **2**, we did the MO calculations of the computational transition models in this electrophilic addition reaction by using the MNDO program for MOPAC and obtained the heat of formation of the stable transition models **A**, **B**, **C**, and **D**. To simplify the calculations, $-O^-$ Li^+ and the substituted phenyl moiety were treated as $-O^-$ and an unsubstituted phenyl moiety, respectively. The stable transition models in the electrophilic attack on the enolate from the upper face [structure **A** and **C**], which would give the *trans*-isomer **1**, are estimated to be more stable than those from the lower face [structure **B** and **D**], which would give the *cis*-isomer **1'**. Especially, the transition model **A** is about 2 kcal mol^{-1} more stable than the transition models **B** and **D**. These results indicate that



Scheme 1.

the electrophilic attack of a proton on the metal enolate **2** would give **1** in about 92% diastereomeric excess (Fig. 2). The obtained results encouraged us to examine our working hypothesis. Our experiment began with synthesis of the α-benzylidene-β-benzyl-γ-butyrolactone **3**. Aldol reaction of the lithium enolate generated from the β-benzyl-γ-butyrolactone **4** and LDA with a substituted benzaldehyde in THF at -78 °C gave a mixture of the two diastereomers (**5**). Without isolation of **5**, the crude **5** was acetylated with Ac_2O and Et_3N in the presence of a catalytic amount of DMAP in THF at room temperature to afford **6** in good yields. On treatment of **6** with two equivalents of NaH in THF at room temperature, **3**[8] was obtained in good yields (89—91% from **4**): the stereoisomer of **3** [(*Z*)-isomer] was not formed in this reaction (Scheme 2).



Scheme 2.

The reducing systems consisting of a metal hydride and a transition metal halide have been used for reduction of the C=C functionality of α,β-unsaturated carbonyl compounds. Although sodium borohydride-transition metal halide reagents have been widely used in reduction of various organic functional groups, e.g., nitrile, nitro compound, azide, hydroperoxide, and alkene, the reaction mechanism is still ambiguous. Pfaltz and co-workers, however, have reported that sodium borohydride–$CoCl_2$ reagent reduced the C=C functionality of α,β-unsaturated carbonyl compounds in a 1,4-hydrogenation manner, that is, conjugate addition of a hydride followed by protonation on the resulting metal enolate.[9,10] On the basis of their proposal, we reduced **3** with sodium borohydride in the presence of the transition metal halides such as $CuCl_2$,[11] $CoCl_2$,[9,10a,12] and $NiCl_2$[10c,13] (Table 1). Reduction of **3** with $NaBH_4$–$CuCl_2$was first examined using **3a** as a representative example. Thus, $NaBH_4$ (4 equiv) was added portionwise to a solution of **3a** and

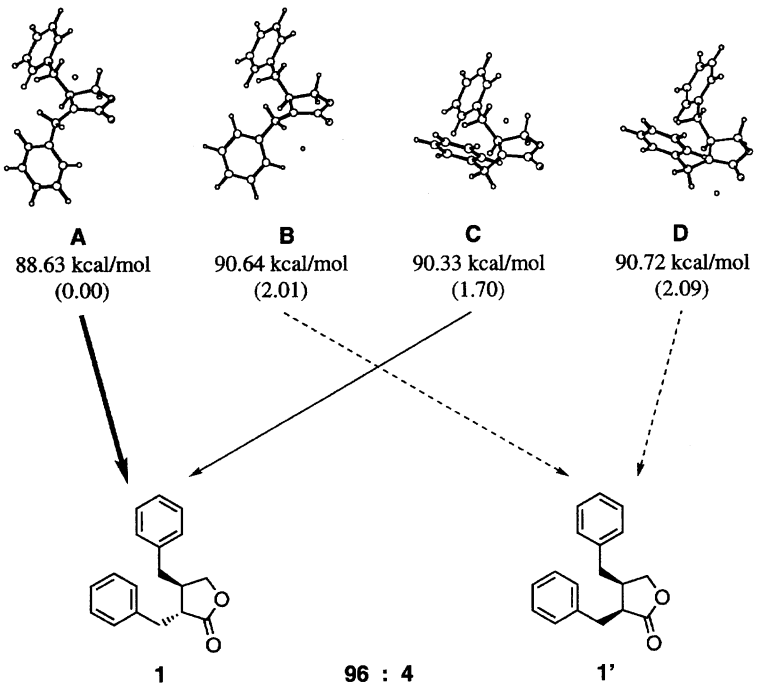


Fig. 2. Heats of formation of the transition structure **A**—**D**.

Table 1. Reduction of **3** with $NaBH_4$-Transition Metal Chloride[a)]

$$\mathbf{3} \xrightarrow[\text{THF–MeOH}]{\text{NaBH}_4\text{–MCl}_2} \mathbf{1}+\mathbf{1}'$$

0 °C

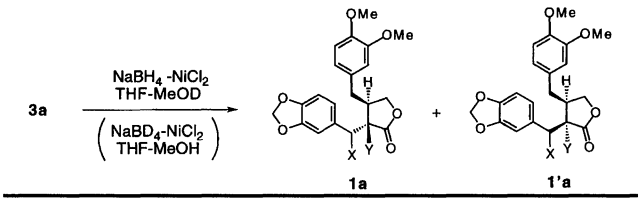
Entry	Substrate	M	Yield/%[b)] (1+1′)	Ratio (1/1′)
1	**3a**	Cu	93	85/15[c)]
2	**3a**	Co	82	79/21[c)]
3	**3a**	Ni	95	94/6[c)]
4	**3b**	Ni	89	93/7[c)]
5	**3c**	Ni	92	97/3[c)]
6	**3d**	Ni	90	92/8[d)]

a) The reaction was carried out in THF–MeOH (4 : 1) at 0 °C. b) Isolated yield. c) The ratio was determined by HPLC analysis. d) The ratio was determined by 200 MHz ^{1}H NMR analysis.

$CuCl_2$ (1 equiv) in THF–MeOH (4 : 1) at 0 °C. After stirring for one hour at 0 °C, the black precipitate was filtered off and the filtrate was concentrated in vacuo. A mixture of **1a** and the *cis*-isomer **1′a** was obtained in 93% yield; the ratio of **1a** and **1′a** being 85 : 15, which was identified by the HPLC analysis (Entry 1 in Table 1).[14)] We next examined the reduction of **3a** with $NaBH_4$–$CoCl_2$ and $NaBH_4$–$NiCl_2$. In the case of $NaBH_4$–$CoCl_2$, both the yield and the stereoselectivity were significantly lowered (Entry 2). On the other hand, the use of $NaBH_4$–$NiCl_2$ heightened the yield to 95% and the ratio of **1a** and **1′a** was greatly improved to 94 : 6 (Entry 3). In this reaction, there is a possibility that *cis*-dibenzyllactone **1′a** initially formed and then isomerized to **1a** under the reduction conditions. Thus, we examined whether isomerization of **1′a** to **1a** occurred. Treatment of **1′a**, which was synthesized stereoselectively by hydrogenation of **3a** under a H_2 atmosphere (1 atm) in the presence of Pd on charcoal, under the same reaction conditions resulted in recovery of **1′a** in quantitative yield. These results indicate that the reduction presumably proceeded via the stereoselective protonation to the metal enolate **2** generated by conjugate addition of a hydride to **3**. The satisfactory results obtained in the use of $NaBH_4$–$NiCl_2$ prompted us to apply this system to reduction of **3b—d**. Almost the same chemical yield and stereoselectivity were obtained in each case (Entries 4, 5, and 6).

To clarify the mechanism of the reduction by the use of $NaBH_4$–$NiCl_2$, we examined the reduction of **3a** in both $NaBD_4$–$NiCl_2$/THF–MeOH and $NaBH_4$–$NiCl_2$/THF–MeOD systems. The results were shown in Table 2. Reduction of **3a** with $NaBD_4$–$NiCl_2$in THF–MeOH gave **1a** and **1′a** in 93% yield (**1a** : **1′a**=93 : 7) with 72% deuterium at the β-position (X) and 11% deuterium at the α-position (Y). On the other hand, reduction of **3a** with $NaBH_4$–$NiCl_2$ in THF–MeOD gave **1a** and **1′a** in 89% yield (**1a** : **1′a**=93 : 7) with 22% deuterium at the β-position (X) and 81% deuterium at the α-position (Y). These results indicate that the hydride (deuteride) was mainly incorporated from $NaBH_4$ ($NaBD_4$) at the β-position (X) and a proton (deuteron) from MeOH (MeOD) at the α-position (Y).

Table 2. Deuteration Study of **3a** Using $NaBD_4$–$NiCl_2$/THF–MeOH or $NaBH_4$–$NiCl_2$/THF–MeOD



Reagent/Solvent	D incorporation/%[a)] X	Y	Yield/%[b)] (1a+1′a)	Ratio[c)] (1a/1′a)
$NaBD_4$–$NiCl_2$/MeOH	72	11	93	93/7
$NaBH_4$–$NiCl_2$/MeOD	22	81	89	93/7

a) Determined by 200 MHz ^{1}H NMR. b) Isolated yield. c) Determined by HPLC analysis.

On the basis of the results described above, we concluded that the reduction would proceed through the following two steps: (a) addition of a hydride derived from the transient metal hydride species to the benzylic position of the α-benzylidene group leading to the metal enolate **2** and (b) following stereoselective protonation on the metal enolate **2** which takes place predominantly from the less hindered β-face due to the shielding effect of the phenyl moiety of the α-benzyl group induced by 1,3-allylic strain.

As described above, we have developed a novel method for the stereoselective synthesis of *trans*-α,β-dibenzyl-γ-butyrolactones **1**. The reaction is found to proceed via the conjugate addition of a hydride and the stereoselective protonation of the resulting metal enolate **2**; the stereoselectivity is brought about by the conformational rigidity of the phenyl moiety of the α-benzyl group induced by 1,3-allylic strain. Because of the efficiency and simplicity, this method should find wide application in the synthesis of this series and other related series of lignans.

Experimental

General Considerations. All melting points were measured on a Yamato MP 21 and are uncorrected. IR spectra were obtained using a Perkin–Elmer 1640 infrared spectrometer. ^{1}H NMR (200 MHz) spectra were recorded on a Bruker AC-200 instrument using Me_4Si as the internal standard. *J* values are given in Hz. Mass spectra were recorded at 70 eV (Hitachi M-2000A). HPLC analyses were done with Shiseido Capcellpac C18 (SG 120, S-5 μm, 4.6×150 mm) and a flow rate of 0.5 mL min^{-1}. Column chromatography was done with silica gel (Merck 7734 and 9385, Kiesel gel 60, 230—400 mesh). THF was dried over 4 Å molecular sieves and used without further purification. All other solvents were used as received.

Computational Methods. Semiempirical molecular orbital calculations were done using MNDO Hamiltonian implemented in MOPAC 5.0.[15)] Conformational analysis of the enolate was conducted using the command SEARCH in SYBYL[16)] with TRIPOS force field in the same manner as that previously reported. As the starting structure of a computational transition model, a proton atom (H^+) was put 2.5 Å above or below the α-carbon (C_α) of an enolate[17)] for each conformer so that the angle of $H^+\cdots C_\alpha{=}C_\beta$ became 90°. Then only the distance of $H^+\cdots C_\alpha$ was constrained and the rest of the geometry was optimized.

Synthesis of β-Benzyl-γ-butyrolactones 4: Typical Procedure. To a solution of *t*-BuOK (67.6 g, 0.602 mol) in *t*-BuOH (600 cm^3) were added veratraldehyde (100 g, 0.602 mol) and dimethyl succinate (80.9 cm^3, 0.602 mol) below 40 °C. After stirring for 30 min, the mixture was poured into water and extracted with *i*-Pr_2O. The aqueous layer was acidified with concd HCl and extracted with AcOEt. The organic layer was washed with water, then brine, and dried over $MgSO_4$. Evaporation of the solvent provided the veratrylidene half ester as a yellowish solid, which was collected by Et_2O (94.0 g, 56%). The yellowish solid (75.0 g, 0.267 mol) was suspended in MeOH (800 cm^3) and stirred under nitrogen. To this mixture was added 10% palladium on charcoal (4.0 g), and the mixture was stirred under hydrogen at atmospheric pressure for 6 h. Filtration and evaporation gave the veratryl half ester as a white solid, which was collected by Et_2O (70.0 g, 93%). The potassium salt was prepared by addition of ethanolic *t*-BuOK (27.8 g, 0.248 mol in 600 cm^3 of EtOH) to a suspension of the veratryl half ester in EtOH (600 cm^3) until basic to phenolphthalein. Powdered anhydrous $CaCl_2$ (100 g, 0.90 mol) was dissolved in anhydrous EtOH (800 cm^3) and cooled to −10 °C. A solution of $NaBH_4$ (70.0 g, 1.85 mol) in the same solvent (1800 cm^3) was added over 1 h, with continual stirring for further 30 min at −10 °C, followed by addition of a solution of the potassium salt in EtOH over 1 h at −78 °C and the mixture was stirred for 12 h at room temperature. The solvent was evaporated, and the residue was dissolved in water and $CHCl_3$. The solution was acidified by concd HCl and refluxed for 30 min. The cooled reaction mixture was separated, and the organic layer was washed with water and brine, and dried over $MgSO_4$. Evaporation of the solvent provided lactone as a yellowish oil, which was purified by silica-gel column chromatography using hexane/AcOEt (1 : 1) as an eluent to afford **4a** (58.2 g, 90%) as a colorless oil.

β-(3,4-Dimethoxybenzyl)-γ-butyrolactone (4a). 47% yield from veratraldehyde; IR (film) 1778 cm^{-1}; ^1H NMR ($CDCl_3$) δ= 2.29 (dd, 1H, *J*=6.5, 17.4 Hz), 2.61 (dd, 1H, *J*=7.8, 17.4 Hz), 2.65—2.98 (m, 3H), 3.87 (s, 3H), 3.88 (s, 3H), 4.04 (dd, 1H, *J*=5.6, 9.0 Hz), 4.34 (dd, 1H, *J*=6.6, 9.1 Hz), 6.67 (s, 1H), 6.69 (dd, 1H, *J*=1.9, 7.9 Hz), 6.82 (d, 1H, *J*=7.9 Hz); MS *m/z* (rel intensity, %) 236 (M^+; 57), 151 (100). Anal. Found: C, 67.92; H, 5.98%. Calcd for $C_{13}H_{16}O_4$: C, 68.10; H, 5.99%.

The lactone **4b** was synthesized by the same procedure described above.

β-(3,4,5-Trimethoxybenzyl)-γ-butyrolactone (4b). 59% yield from 3,4,5-trimethoxybenzaldehyde; mp 98—99 °C (AcOEt–hexane); IR (KBr) 1711 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.30 (dd, 1H, *J*=6.5, 17.3 Hz), 2.64 (dd, 1H, *J*=7.9, 17.3 Hz), 2.68—2.98 (m, 3H), 3.83 (s, 3H), 3.85 (s, 6H), 4.06 (dd, 1H, *J*=5.6, 9.1 Hz), 4.36 (dd, 1H, *J*=6.6, 9.1 Hz), 6.36 (s, 2H); MS *m/z* (rel intensity, %) 266 (M^+; 50), 151 (73), 135 (100). Anal. Found: C, 63.08; H, 6.53%. Calcd for $C_{14}H_{18}O_5$: C, 63.15; H, 6.81%.

(*E*)-α-(3,4-Methylenedioxybenzylidene)-β-(3,4-dimethoxybenzyl)-γ-butyrolactone (3a). LDA (36.0 mmol) was prepared by addition of butyllithium (1.6 M in hexane (M=mol dm^{-3}), 22.5 cm^3, 36.0 mmol) to a solution of diisopropylamine (5.05 cm^3, 36.0 mmol) in THF (50 cm^3) at −78 °C under nitrogen atmosphere. The mixture was stirred for 20 min at 0 °C, and was recooled to −78 °C. To the mixture was added dropwise **4a** (7.08 g, 30 mmol) in THF (20 cm^3) at the same temperature. After 20 min, 3,4-methylenedioxybenzaldehyde (4.50 g, 30 mmol) in THF (10 cm^3) was added to the mixture, and it was stirred for 1 h at the same temperature. The mixture was quenched by addition of saturated aqueous ammonium chloride. The organic layer was separated and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with water and brine, and dried over $MgSO_4$. Evaporation of the solvent provided the crude product **5d** as an oil. Without isolation of **5a**, the mixture was acetylated with acetic anhydride (3.68 cm^3, 39.0 mmol), triethylamine (5.44 cm^3, 39.0 mmol) and 4-(dimethylamino)pyridine (0.37 g, 3 mmol) in THF (100 cm^3) at room temperature for 5h. The reaction mixture was poured into water, and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with water and brine, and dried over $MgSO_4$. Evaporation of the solvent provided the acetylated product **6a** after purification by silica-gel column chromatography using $CHCl_3$/AcOEt (20 : 1) as an eluent. The acetylated product was dissolved in THF (100 cm^3), and sodium hydride (2.40 g, 60 mmol) was added to the mixture portionwise at 0 °C. The mixture was stirred at room temperature for 12 h, and it was quenched with water, and acidified by 2 M HCl. The aqueous layer was extracted with AcOEt, and the combined organic layer was washed with water and brine, and dried over $MgSO_4$. Evaporation of the solvent provided the *exo*-olefin **3a** as a solid, which was collected by Et_2O (10.1 g, 92%); mp 95—96 °C (AcOEt–hexane); IR (KBr) 1738 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.63 (dd, 1H, *J*=9.9, 14.2 Hz), 3.02 (dd, 1H, *J*=4.4, 14.2 Hz), 3.70—3.91 (m, 1H), 3.86 (s, 3H), 3.88 (s, 3H), 4.20—4.36 (m, 2H), 6.04 (s, 2H), 6.66—6.92 (m, 4H), 7.02—7.14 (m, 2H), 7.51 (d, 1H, *J*=1.8 Hz); MS *m/z* (rel intensity, %) 368 (M^+; 25), 217 (8), 151 (100). Anal. Found: C, 68.44; H, 5.29%. Calcd for $C_{21}H_{20}O_6$: C, 68.47; H, 5.47%.

(*E*)-α-(3,4-Methylenedioxybenzylidene)-β-(3,4,5-trimethoxybenzyl)-γ-butyrolactone (3b). Compound **3b** (27.2 g, 91%) was prepared from **4b** (20.0 g, 75.2 mmol) in the same manner described above: mp 140—141 °C (AcOEt–hexane); IR (KBr) 1747 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.64 (dd, 1H, *J*=9.6, 14.0 Hz), 3.00 (dd, 1H, *J*=4.8, 14.0 Hz), 3.70—3.92 (m, 1H), 3.81 (s, 3H), 3.85 (s, 6H), 4.27—4.37 (m, 2H), 6.03 (s, 2H), 6.41 (s, 2H), 6.86 (d, 1H, *J*=5.8 Hz), 7.02—7.14 (m, 2H), 7.51 (d, 1H, *J*=1.7 Hz); MS *m/z* (rel intensity, %) 398 (M^+; 10), 181 (100). Anal. Found: C, 68.35; H, 5.43%. Calcd for $C_{22}H_{22}O_7$: C, 66.32; H, 5.57%.

(*E*)-α-(3-Methoxy-4-benzyloxybenzylidene)-β-(3,4-dimethoxybenzyl)-γ-butyrolactone (3c). Compound **3c** (9.12 g, 90%) was prepared from **4a** (5.20 g, 22.0 mmol) in the same manner described above; mp 112—113 °C (AcOEt–hexane); IR (KBr) 1749 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.64 (dd, 1H, *J*=10.3, 14.4 Hz), 3.09 (dd, 1H, *J*=4.0, 14.4 Hz), 3.72—3.94 (m, 1H), 3.84 (s, 3H), 3.86 (s, 3H), 3.91 (s, 3H), 4.27 (d, 2H, *J*=4.2 Hz), 5.22 (s, 2H), 6.66 (d, 1H, *J*=1.7 Hz), 6.73 (dd, 1H, *J*=1.8, 8.1 Hz), 6.81 (d, 1H, *J*=8.1 Hz), 6.94 (d, 1H, *J*=8.2 Hz), 7.08—7.21 (m, 2H), 7.29—7.49 (m, 5H), 7.53 (d, 1H, *J*=1.7 Hz); MS *m/z* (rel intensity, %) 460 (M^+; 26), 309 (45), 151 (100), 91 (99). Anal. Found: C, 73.34; H, 6.02%. Calcd for $C_{28}H_{28}O_6$: C, 73.03; H, 6.13%.

(*E*)-α-(3,4,5-Trimethoxybenzylidene)-β-(3,4,5-trimethoxybenzyl)-γ-butyrolactone (3d). Compound **3d** (37.0 g, 83%) was prepared from **4b** (26.6 g, 100 mmol) in the same manner described above: mp 110—111 °C (AcOEt–hexane) [Lit,[3f] mp 106—107 °C (ether)]; IR (KBr) 1751 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.65 (dd, 1H, *J*=10.3, 14.4 Hz), 3.10 (dd, 1H, *J*=4.4, 14.4 Hz), 3.78—3.91 (m, 1H), 3.82 (s, 3H), 3.83 (s, 6H), 3.89 (s, 6H), 3.91 (s, 3H), 4.25—4.40 (m, 2H), 6.38 (s, 2H), 6.82 (s, 2H), 7.54 (d, 1H, *J*=1.8 Hz); MS *m/z* (rel intensity, %) 444 (M^+; 12), 263 (18), 181 (100). Anal. Found: C, 64.70; H, 6.28%. Calcd for $C_{24}H_{28}O_8$: C, 64.85; H, 6.35%.

Reduction of α-Benzylidene-γ-butyrolactones (3). *trans*-α-(3,4-Methylenedioxybenzyl)-β-(3,4-dimethoxybenzyl)-γ-butyrolactone (1a). To a solution of **3a** (920 mg, 2.50 mmol) and $NiCl_2 \cdot 6H_2O$ (594 mg, 2.50 mmol) in THF (20 cm^3)–MeOH

(4 cm^3) was added portionwise $NaBH_4$ (378 mg, 10.0 mmol) with vigorous stirring under a nitrogen atmosphere at 0 °C. After 1 h, the insoluble materials were filtered off and the filtrate was concentrated in vacuo. The residue was dissolved in $CHCl_3$ and washed with 2 M HCl aq, water and brine, and dried over $MgSO_4$. Evaporation of the solvent afforded the mixture of **1a** and **1′a** (880 mg, 95%) as a white solid: The ratio of **1a** and **1′a** being determined by HPLC analysis (CH_3CN : H_2O=40 : 60). *trans*-Dibenzyllactone **1a** was purified by single recrystallization from AcOEt–hexane to give pure **1a**; mp 107—108 °C (AcOEt–hexane); IR (KBr) 1767 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.37—2.73 (m, 4H), 2.85 (dd, 1H, J=6.4, 14.0 Hz), 2.97 (dd, 1H, J=4.9, 13.9 Hz), 3.83 (s, 3H), 3.86 (s, 3H), 3.88 (dd, 1H, J=7.0, 9.4 Hz), 4.15 (dd, 1H, J=6.8, 9.3 Hz), 5.90—5.99 (m, 2H), 6.48 (d, 1H, J=1.9 Hz), 6.52—6.61 (m, 1H), 6.57—6.67 (br. s, 2H), 6.69—6.83 (m, 2H); MS *m/z* (rel intensity, %) 370 (M^+; 42), 151 (72), 135 (100). Anal. Found: C, 67.82; H, 5.81%. Calcd for $C_{21}H_{22}O_6$: C, 68.10; H, 5.99%. Reduction of **3a** (920 mg, 2.50 mmol) in the presence of $CuCl_2 \cdot 2H_2O$ or $CoCl_2 \cdot 6H_2O$ instead of $NiCl_2 \cdot 6H_2O$ was done in the same manner described above to afford a mixture of **1a** and **1′a** [862 mg (93%), 765 mg (82%)], respectively. The ratio of **1a** and **1′a** was measured by HPLC analysis (CH_3CN : H_2O=40 : 60) of an unpurified reaction mixture.

***trans*-α-(3,4-Methylenedioxybenzyl)-β-(3,4,5-trimethoxybenzyl)-γ-butyrolactone (1b).** Reduction of **3b** (995 mg, 2.50 mmol) was done in the same manner described above to furnish a mixture of **1b** and **1′b** (890 mg, 89%). The ratio of **1b** and **1′b** was measured by HPLC analysis (CH_3CN : H_2O=40 : 60) of an unpurified reaction mixture. Pure **1b** was obtained by single recrystallization from AcOEt; mp 110—111 °C (AcOEt); IR (KBr) 1763 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.41—2.68 (m, 4H), 2.85 (dd, 1H, J=6.3, 13.8 Hz), 2.99 (dd, 1H, J=4.6, 13.8 Hz), 3.82 (s, 9H), 3.90 (dd, 1H, J=6.8, 9.2 Hz), 4.19 (dd, 1H, J=6.6, 9.4 Hz), 5.90—5.98 (m, 2H), 6.20 (s, 2H), 6.58 (dd, 1H, J=1.6, 9.2 Hz), 6.61 (s, 1H), 6.72 (d, 1H, J=8.1 Hz); MS *m/z* (rel intensity, %) 400 (M^+; 92), 182 (100), 135 (93). Anal. Found: C, 65.95; H, 5.79%. Calcd for $C_{22}H_{24}O_7$: C, 65.99; H, 6.04%.

***trans*-α-(3-Methoxy-4-benzyloxybenzyl)-β-(3,4-dimethoxybenzyl)-γ-butyrolactone (1c).** Reduction of **3c** (1.15 g, 2.5 mmol) was done in the same manner described above to furnish a mixture of **1c** and **1′c** (1.06 g, 92%). The ratio of **1c** and **1′c** was measured by HPLC analysis (CH_3CN : H_2O=40 : 60) of an unpurified reaction mixture. Pure **1c** was obtained by single recrystallization from AcOEt–hexane; mp 94—95 °C (AcOEt–hexane); IR (KBr) 1769 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.42—2.68 (m, 4H), 2.90—3.00 (m, 2H), 3.80 (s, 3H), 3.84 (s, 3H), 3.85 (s, 3H), 3.80—3.92 (m, 1H), 4.07—4.18 (m, 1H), 5.13 (s, 2H), 6.47 (d, 1H, J=1.9 Hz), 6.52 (dd, 1H, J=1.9, 8.1 Hz), 6.59 (dd, 1H, J=1.9, 8.1 Hz), 6.71 (d, 1H, J=2.4 Hz), 6.74 (d, 1H, J=9.4 Hz), 6.79 (d, 1H, J=8.2 Hz), 7.25—7.48 (m, 5H); MS *m/z* (rel intensity, %) 462 (M^+; 70), 247 (20), 151 (77), 91 (100). Anal. Found: C, 72.44; H, 6.24%. Calcd for $C_{28}H_{30}O_6$: C, 72.71; H, 6.54%.

***trans*-α,β-Bis(3,4,5-trimethoxybenzyl)-γ-butyrolactone (1d).** Reduction of **3d** (1.11 g, 2.5 mmol) was carried out in the same manner described above to furnish a mixture of **1d** and **1′d** (1.00 g, 90%). The ratio of **1d** and **1′d** was measured by 200 MHz ^1H NMR analysis of an unpurified reaction mixture. Pure **1d** was obtained by single recrystallization from AcOEt; mp 91—92 °C (AcOEt) [Lit,[10f] mp 87—90 °C (ether)]; IR (KBr) 1769 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.44—2.75 (m, 4H), 2.97 (br.d, 2H, J=5.5 Hz), 3.80 (s, 6H), 3.81 (s, 6H), 3.82 (s, 6H), 3.89 (dd, 1H, J=7.5, 9.4 Hz), 4.19 (dd, 1H, J=6.8, 9.3 Hz), 6.22 (s, 2H), 6.39 (s, 2H); MS *m/z* (rel intensity, %) 446 (M^+; 75), 181 (100). Anal. Found: C, 64.38; H, 6.80%. Calcd for $C_{24}H_{30}O_8$: C, 64.56; H, 6.77%.

***cis*-α-(3,4-Methylenedioxybenzyl)-β-(3,4-dimethoxybenzyl)-γ-butyrolactone (1′a).** The *exo*-olefin **3a** (8.88 g, 24.1 mmol) was dissolved in a mixture of THF (80 cm^3) and MeOH (40 cm^3), and palladium on charcoal catalyst (10% Pd, 500 mg) was added. The mixture was stirred under an H_2 atmosphere (1 atm, room temperature) for 4 h followed by filtration and evaporation to give a *cis*-dibenzyllactone **1′a** (8.31 g, 93%) as a sole product: mp 103—104 °C (AcOEt–hexane); IR (KBr) 1771 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.32 (dd, 1H, J=12.3, 13.3 Hz), 2.59—2.78 (m, 1H), 2.76 (dd, 1H, J=10.3, 14.6 Hz), 2.93 (dd, 1H, J=9.8, 13.6 Hz), 2.98—3.12 (m, 1H), 3.23 (dd, 1H, J=4.7, 14.5 Hz), 3.84 (s, 3H), 3.85 (s, 3H), 3.96—4.13 (m, 2H), 5.96 (s, 2H), 6.53 (d, 1H, J=1.9 Hz), 6.61 (dd, 1H, J=1.9, 8.1 Hz), 6.70—6.85 (m, 4H); MS *m/z* (rel intensity, %) 370 (M^+; 60), 151 (59), 135 (100). Anal. Found: C, 68.04; H, 5.79%. Calcd for $C_{21}H_{22}O_6$: C, 68.10; H, 5.99%.

Isomerization of *cis*-Dibenzyllactone (1′a) to *trans*-Dibenzyllactone (1a). To a solution of **1′a** (370 mg, 1.00 mmol) and $NiCl_2 \cdot 6H_2O$ (238 mg, 1.00 mmol) in THF (8 cm^3)–MeOH (1.5 cm^3) was added portionwise $NaBH_4$ (152 mg, 4.00 mmol) with vigorous stirring under a nitrogen atmosphere at 0 °C. After 1 h, insoluble materials were filtered off and the filtrate was concentrated in vacuo. The residue was dissolved in $CHCl_3$ and washed with 2 M HCl aq, water and brine, and dried over $MgSO_4$. Evaporation of the solvent afforded the crude product as a solid. The ratio of **1a** and **1′a** was measured by HPLC analysis (CH_3CN : H_2O=40 : 60) of an unpurified reaction mixture.

Deuteration Study of α-Benzylidenelactone 3a with $NaBD_4$–$NiCl_2$ in THF–MeOH. To a solution of **3a** (920 mg, 2.50 mmol) and $NiCl_2$ (324 mg, 2.50 mmol) in THF (20 cm^3)–MeOH (4 cm^3) was added portionwise $NaBD_4$ (418 mg, 10.0 mmol) with vigorous stirring under a nitrogen atmosphere at 0 °C. After 1 h, the insoluble materials were filtered off and the filtrate was concentrated in vacuo. The residue was dissolved in $CHCl_3$ and washed with 2 M HCl aq, water, and brine, and dried over $MgSO_4$. Evaporation of the solvent afforded a mixture of **1a** and **1′a** (865 mg, 93%) as a solid, which was purified by recrystallization from AcOEt–hexane. The ratio of **1a** and **1′a** was measured by HPLC analysis (CH_3CN : H_2O=40 : 60) and the ratio of the incorporation of deuterium was measured by 200 MHz ^1H NMR analysis of an unpurified reaction mixture.

Deuteration Study of α-Benzylidenelactone 3a with $NaBH_4$–$NiCl_2$ in THF–MeOD. To a solution of **3a** (920 mg, 2.50 mmol) and $NiCl_2$ (324 mg, 2.50 mmol) in THF (20 cm^3)–MeOD (4 cm^3) was added portionwise $NaBH_4$ (378 mg, 10.0 mmol) with vigorous stirring under a nitrogen atmosphere at 0 °C. After 1 h, the insoluble materials were filtered off and the filtrate was concentrated in vacuo. The residue was dissolved in $CHCl_3$ and washed with 2 M HCl aq, water, and brine, and dried over $MgSO_4$. Evaporation of the solvent afforded the mixture of **1a** and **1′a** (830 mg, 89%) as a solid, which was purified by recrystallization from AcOEt–hexane. The ratio of **1a** and **1′a** was measured by HPLC analysis (CH_3CN : H_2O=40 : 60) and the ratio of the incorporation of deuterium was measured by 200 MHz ^1H NMR analysis of an unpurified reaction mixture.

References

1) a) C. B. S. Rao, "Chemistry of Lignans," Andhra University Press, Andhra Pradesh (1978); b) D. C. Ayres and J. D. Loike, "Lignans," Cambridge Univ. Press, Cambridge (1990); c) R. S.

Ward, *Chem. Soc. Rev.*, **11**, 75 (1982); d) R. S. Ward, *Tetrahedron*, **46**, 5029 (1990); e) S. Yamamura, *Synth. Org. Chem. Jpn.*, **43**, 583 (1985); f) H. Ohmizu and T. Iwasaki, *Synth. Org. Chem. Jpn.*, **53**, 593 (1995).

2) a) E. Bianchi, M. E. Caldwell, and J. R. Cole, *J. Pharm. Sci.*, **57**, 696 (1968); b) P. B. McDaniel and J. R. Cole, *J. Pharm. Sci.*, **61**, 1992 (1972); c) S. R. Stitch, J. K. Toumba, M. B. Groen, C. W. Funke, J. Leemhuis, J. Vink, and G. F. Woods, *Nature*, **287**, 738 (1980); d) K. D. R. Setchel, A. M. Lawson, F. L. Mitchell, H. Adlercreutz, D. N. Kirk, and M. Axelson, *Nature*, **287**, 740 (1980); e) M. Axelson, J. Sjöall, B. E. Gustafsson, and K. D. R. Setchel, *Nature*, **298**, 659 (1982); f) K. Tomioka, H. Mizuguchi, and K. Koga, *Chem. Pharm. Bull.*, **30**, 4304 (1982); g) P. Braquet and J. J. Godfroid, *Trends. Pharm. Sci.*, **1986**, 397; h) G. Plante, C. Prévost, A. Chainey, P. Braquet, and P. Sirois, *Am. J. Physiol.*, **253**, R375 (1987).

3) a) P. A. Ganeshpure and R. Stevenson, *J. Chem. Soc., Perkin Trans. 1*, **1981**, 1681; b) G. E. Schneiders and R. Stevenson, *J. Chem. Soc., Perkin Trans. 1*, **1982**, 999; c) K. Tomioka, T. Ishiguro, and K. Koga, *Chem. Pharm. Bull.*, **33**, 4333 (1985); d) E. Brown and A. Daugan, *Heterocycles*, **26**, 1169 (1987); e) K. Lalami, R. Dahl, and E. Brown, *Heterocycles*, **27**, 1131 (1988); f) Y. Landais, J. -P. Robin, and A. Lebrun, *Tetrahedron*, **47**, 3787 (1991); g) H. Yoda, H. Kitayama, T. Katagiri, and K. Takabe, *Tetrahedron*, **48**, 3313 (1992).

4) J. L. Belletire and D. F. Fry, *J. Org. Chem.*, **52**, 2549 (1987).

5) a) A. Pelter, P. Satyanarayana, and R. S. Ward, *Tetrahedron Lett.*, **22**, 1549 (1981); b) A. Pelter, R. S. Ward, D. M. Jones, and P. Maddocks, *Tetrahedron : Asymmetry*, **3**, 239 (1992).

6) a) M. Takahashi, T. Kuroda, T. Ogiku, H. Ohmizu, K. Kondo, and T. Iwasaki, *Heterocycles*, **36**, 1867 (1993); b) M. Takahashi, T. Kuroda, T. Ogiku, H. Ohmizu, K. Kondo, and T. Iwasaki, *Heterocycles*, **36**, 1867 (1993); c) T. Kuroda, M. Takahashi, T. Ogiku, H. Ohmizu, T. Nishitani, K. Kondo, and T. Iwasaki, *J. Org. Chem.*, **59**, 7353 (1994); d) T. Ogiku, S. Yoshida, H. Ohmizu, and T. Iwasaki, *J. Org. Chem.*, **60**, 1148 (1995); e) T. Ogiku, S. Yoshida, H. Ohmizu, and T. Iwasaki, *J. Org. Chem.*, **60**, 4585 (1995).

7) a) Y. Moritani, T. Ukita, T. Nishitani, M. Seki, and T. Iwasaki, *Tetrahedron Lett.*, **31**, 3615 (1990); b) Y. Moritani, C. Fukushima, T. Ogiku, T. Ukita, T. Miyagishima, and T. Iwasaki, *Tetrahedron Lett.*, **34**, 2787 (1993); c) Y. Moritani, T. Ukita, H. Ohmizu, and T. Iwasaki, *J. Chem. Soc., Chem. Commun.*, **1995**, 671.

8) Stereochemistry (*E* or *Z*) of the α-benzylidene group of **3** was determined on the basis of the chemical shift of the vinylic proton in 200 MHz ^{1}H NMR spectra. Banerji et al. and von Wartburg et al. have reported that the vinylic hydrogen resonances of the *E*-α-arylidene-γ-butyrolactones always appear at about δ=7.50 in ^{1}H NMR spectra: See, a) von M. Kuhn and A. von Wartburg, *Helv. Chim. Acta*, **50**, 1546 (1967); b) J. Banerji, B. Das, A. Chatterjee, and J. N. Shoolery, *Phytochemistry*, **23**, 2323 (1984).

9) a) P. von Matt and A. Pfaltz, *Tetrahedron : Asymmetry*, **2**, 691 (1991); b) A. Pfaltz, *Acc. Chem. Res.*, **26**, 339 (1993).

10) Besides Pfaltz's proposal, three other mechanisms have been proposed, see: a) S. W. Heinzman and B. Ganem, *J. Am. Chem. Soc.*, **104**, 6801 (1982); b) M. Narisada, I. Horibe, F. Watanabe, and K. Takeda, *J. Org. Chem.*, **54**, 5308 (1989); c) N. Abe, F. Fujisaki, K. Sumoto, and S. Miyano, *Chem. Pharm. Bull.*, **39**, 1167 (1991).

11) J. A. Cowan, *Tetrahedron Lett.*, **27**, 1205 (1986).

12) S. -K. Chung, *J. Org. Chem.*, **44**, 1014 (1979).

13) a) T. Satoh, K. Nanba, and S. Suzuki, *Chem. Pharm. Bull.*, **19**, 817 (1971); b) H. S. P. Rao, K. S. Reddy, K. Turnbull, and Borchers, *Synth. Commun.*, **22**, 1339 (1992); c) T. G. Back, K. Yang, and H. R. Krouse, *J. Org. Chem.*, **57**, 1986 (1992); d) F. Wang, K. Chiba, and M. Tada, *J. Chem. Soc., Perkin Trans. 1*, **1992**, 1897.

14) The structure of **1** and **1′**, obtained by our method reported in this paper, were confirmed by comparison of their 200 MHz ^{1}H NMR spectra with those of the authentic sample of **1** and **1′** that were synthesized by the use of the known methods (It is well documented that benzylation of the β-benzyl-γ-butyrolantones **4** afforded the *trans*-dibenzyllactones **1** exclusively and hydrogenation of the α-benzylidene-β-benzyl-γ-butyrolantones **3** afforded the *cis*-isomers **1′** exclusively: See, Refs. 3c, 3d, 3e, and 3f).

15) MOPAC Ver. 5, J. J. P. Stewart, QCPE #455; Revised as Ver. 5.01 by T. Hirano, for UNIX machines, *JCPE Newsletter*, **1(2)**, 36 (1989).

16) TRIPOS, Inc., 1699 S. Hanley Road, St. Louis, Missouri 63144-2913.

17) Takahashi and Tsuji reported that the stereoselectivity observed in protonation of the metal enolate of 3-alkyl-2-methyl-1-acetylcyclopentene, prepared by conjugate addition of vinyl group, could be rationalized by MM2 calculations. They fixed the position of the proton donor 2.5 Å above or below the α-carbon of the metal enolate, and optimized the geometry for the rest of the system: H. Yamada, K. Shimizu, M. Nisar, T. Takahashi, and J. Tsuji, *Tetrahedron Lett.*, **31**, 2407 (1990).