

Simple Synthesis of *trans*- α,β -Dibenzyl- γ -butyrolactone Lignans by Diastereoselective Reduction of α -Benzylidene- β -benzyl- γ -butyrolactones Using NaBH₄–NiCl₂

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trans- α,β -Dibenzyl- γ -butyrolactone lignans were synthesized by stereoselective reduction of α -benzylidene- β -benzyl- γ -butyrolactones using NaBH₄–NiCl₂. 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.

Lignans¹⁾ 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 derivatives⁴⁾ 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.

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, $\text{O}^- \text{Li}^+$ 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

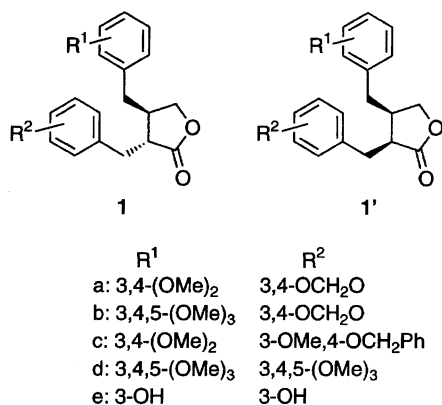
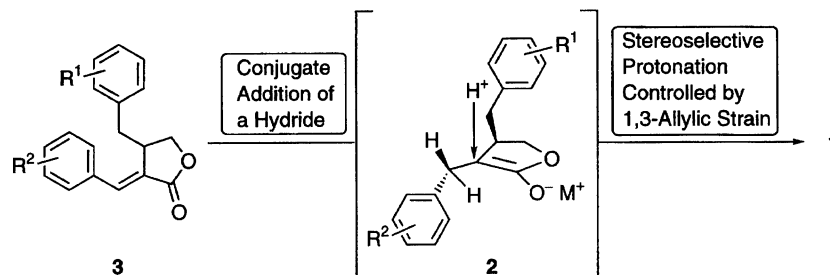
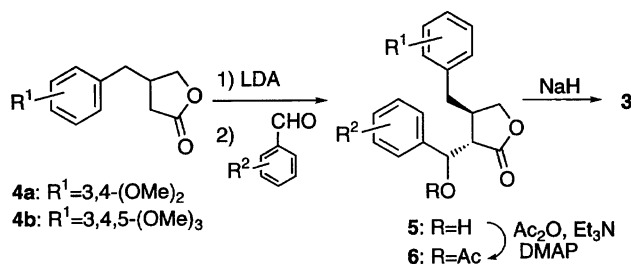


Fig. 1.



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).

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

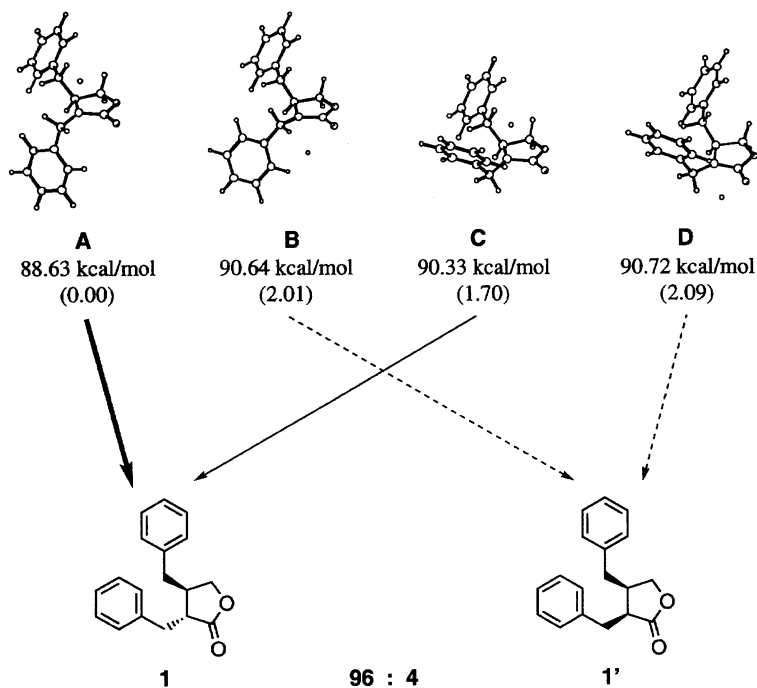


Fig. 2. Heats of formation of the transition structure A—D.

Table 1. Reduction of **3** with NaBH₄-Transition Metal Chloride^{a)}

$$\text{3} \xrightarrow[\text{THF-MeOH, 0 } ^\circ\text{C}]{\text{NaBH}_4\text{-MCl}_2} \text{1} + \text{1}'$$

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)}

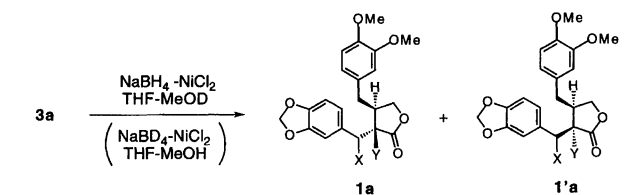
a) The reaction was carried out in THF-MeOH (4:1) at 0 °C.

b) Isolated yield. c) The ratio was determined by HPLC analysis.

d) The ratio was determined by 200 MHz ¹H NMR analysis.

CuCl₂ (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 NaBH₄-CoCl₂ and NaBH₄-NiCl₂. In the case of NaBH₄-CoCl₂, both the yield and the stereoselectivity were significantly lowered (Entry 2). On the other hand, the use of NaBH₄-NiCl₂ 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*-dibenzylactone **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 H₂ 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 NaBH₄-NiCl₂ 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 NaBH₄-NiCl₂, we examined the reduction of **3a** in both NaBD₄-NiCl₂/THF-MeOH and NaBH₄-NiCl₂/THF-MeOD systems. The results were shown in Table 2. Reduction of **3a** with NaBD₄-NiCl₂ 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 NaBH₄-NiCl₂ 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 NaBH₄ (NaBD₄) at the β-position (X) and a proton (deuteron) from MeOH (MeOD) at the α-position (Y).

Table 2. Deuteration Study of **3a** Using NaBD₄-NiCl₂/THF-MeOH or NaBH₄-NiCl₂/THF-MeOD


Reagent/Solvent	D incorporation/% ^{a)}		Yield/% ^{b)} (1a + 1'a)	Ratio ^{c)} (1a / 1'a)
	X	Y		
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 ¹H NMR. b) Isolated yield. c) De-

termined 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. ¹H NMR (200 MHz) spectra were recorded on a Bruker AC-200 instrument using Me₄Si 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 SYBYL¹⁶⁾ 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 enolate¹⁷⁾ for each conformer so that the angle of H⁺...C_α=C_β became 90°. Then only the distance of H⁺...C_α 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 cm³) were added veratraldehyde (100 g, 0.602 mol) and dimethyl succinate (80.9 cm³, 0.602 mol) below 40 °C. After stirring for 30 min, the mixture was poured into water and extracted with *i*-Pr₂O. The aqueous layer was acidified with concd HCl and extracted with AcOEt. The organic layer was washed with water, then brine, and dried over MgSO₄. Evaporation of the solvent provided the veratrylidene half ester as a yellowish solid, which was collected by Et₂O (94.0 g, 56%). The yellowish solid (75.0 g, 0.267 mol) was suspended in MeOH (800 cm³) 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 Et₂O (70.0 g, 93%). The potassium salt was prepared by addition of ethanolic *t*-BuOK (27.8 g, 0.248 mol in 600 cm³ of EtOH) to a suspension of the veratryl half ester in EtOH (600 cm³) until basic to phenolphthalein. Powdered anhydrous CaCl₂ (100 g, 0.90 mol) was dissolved in anhydrous EtOH (800 cm³) and cooled to -10 °C. A solution of NaBH₄ (70.0 g, 1.85 mol) in the same solvent (1800 cm³) 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 CHCl₃. 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 MgSO₄. 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 (CDCl₃) 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 C₁₃H₁₆O₄: 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 (CDCl₃) 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 C₁₄H₁₈O₅: 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 cm³, 36.0 mmol) to a solution of diisopropylamine (5.05 cm³, 36.0 mmol) in THF (50 cm³) 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 cm³) at the same temperature. After 20 min, 3,4-methylenedioxybenzaldehyde (4.50 g, 30 mmol) in THF (10 cm³) 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 MgSO₄. 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 cm³, 39.0 mmol), triethylamine (5.44 cm³, 39.0 mmol) and 4-(dimethylamino)pyridine (0.37 g, 3 mmol) in THF (100 cm³) at room temperature for 5 h. 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 MgSO₄. Evaporation of the solvent provided the acetylated product **6a** after purification by silica-gel column chromatography using CHCl₃/AcOEt (20 : 1) as an eluent. The acetylated product was dissolved in THF (100 cm³), 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 MgSO₄. Evaporation of the solvent provided the *exo*-olefin **3a** as a solid, which was collected by Et₂O (10.1 g, 92%); mp 95–96 °C (AcOEt–hexane); IR (KBr) 1738 cm⁻¹; ¹H NMR (CDCl₃) 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 C₂₁H₂₀O₆: 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 (CDCl₃) 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 C₂₂H₂₂O₇: C, 66.32; H, 5.57%.

(*E*)- α -(3-Methoxy-4-benzoyloxybenzylidene)- 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 (CDCl₃) 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 C₂₈H₂₈O₆: 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 (CDCl₃) 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 C₂₄H₂₈O₈: 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 NiCl₂·6H₂O (594 mg, 2.50 mmol) in THF (20 cm³)–MeOH

(4 cm³) was added portionwise NaBH₄ (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 CHCl₃ and washed with 2 M HCl aq, water and brine, and dried over MgSO₄. 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 (CH₃CN : H₂O=40 : 60). *trans*-Dibenzylactone **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 (CDCl₃) 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 C₂₁H₂₂O₆: C, 68.10; H, 5.99%. Reduction of **3a** (920 mg, 2.50 mmol) in the presence of CuCl₂ · 2H₂O or CoCl₂ · 6H₂O instead of NiCl₂ · 6H₂O 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 (CH₃CN : H₂O=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 (CH₃CN : H₂O=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 (CDCl₃) 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 C₂₂H₂₄O₇: 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 (CH₃CN : H₂O=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 (CDCl₃) 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 C₂₈H₃₀O₆: 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 (CDCl₃) 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 C₂₄H₃₀O₈: 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 cm³) and MeOH (40 cm³), and palladium on charcoal catalyst (10% Pd, 500 mg) was added. The mixture was stirred under an H₂ atmosphere (1 atm, room temperature) for 4 h followed by filtration and evaporation to give a *cis*-dibenzylactone **1'a** (8.31 g, 93%) as a sole product: mp 103–104 °C (AcOEt–hexane); IR (KBr) 1771 cm⁻¹; ¹H NMR (CDCl₃) 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 C₂₁H₂₂O₆: C, 68.10; H, 5.99%.

Isomerization of *cis*-Dibenzylactone (1'a) to *trans*-Dibenzylactone (1a). To a solution of **1'a** (370 mg, 1.00 mmol) and NiCl₂ · 6H₂O (238 mg, 1.00 mmol) in THF (8 cm³)–MeOH (1.5 cm³) was added portionwise NaBH₄ (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 CHCl₃ and washed with 2 M HCl aq, water and brine, and dried over MgSO₄. Evaporation of the solvent afforded the crude product as a solid. The ratio of **1a** and **1'a** was measured by HPLC analysis (CH₃CN : H₂O=40 : 60) of an unpurified reaction mixture.

Deuteration Study of α-Benzylidenelactone 3a with NaBD₄–NiCl₂ in THF–MeOH. To a solution of **3a** (920 mg, 2.50 mmol) and NiCl₂ (324 mg, 2.50 mmol) in THF (20 cm³)–MeOH (4 cm³) was added portionwise NaBD₄ (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 CHCl₃ and washed with 2 M HCl aq, water, and brine, and dried over MgSO₄. 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 (CH₃CN : H₂O=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 NaBH₄–NiCl₂ in THF–MeOD. To a solution of **3a** (920 mg, 2.50 mmol) and NiCl₂ (324 mg, 2.50 mmol) in THF (20 cm³)–MeOD (4 cm³) was added portionwise NaBH₄ (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 CHCl₃ and washed with 2 M HCl aq, water, and brine, and dried over MgSO₄. 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 (CH₃CN : H₂O=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 ^1H 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 $\delta=7.50$ in ^1H 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 ^1H 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 -butyrolactones **4** afforded the trans-dibenzylactones **1** exclusively and hydrogenation of the α -benzylidene- β -benzyl- γ -butyrolactones **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).