6922 *J. Org. Chem.* **1996,** *61,* 6922−6930

Stereoselective Syntheses of *Cis*- and *Trans*-Isomers of α-Hydroxy-α,*β*-dibenzyl-*γ*-butyrolactone Lignans: New Syntheses of (±)-Trachelogenin and (±)-Guayadequiol

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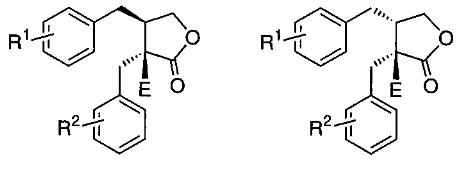
Received January 30, 1996⊗

Cis- and *trans*-isomers of α-hydroxy-α,*β*-dibenzyl-*γ*-butyrolactone lignans **1a**,**d**−**g** and **2a**,**c**,**d** were stereoselectively synthesized in good yields based on the electrophilic addition to the metal enolate of α-benzyl-*γ*-butyrolactone derivatives **1l**−**o** and **3** as a key step. This method was applied to the syntheses of (±)-trachelogenin and (±)-guayadequiol, representative examples of the *trans*- and *cis*-isomers of α-hydroxy-α,*β*-dibenzyl-*γ*-butyrolactone lignan series.

Introduction

Lignans of the α,*β*-dibenzyl-*γ*-butyrolactone series[1] having a hydroxyl group at the α-position, e.g., trachelogenin (**1a**),[2] wikstromol (**1b**),[3] and guayadequiol (**2c**),[4] are widely distributed in plants and have attracted considerable interest since the discovery of their intriguing biological activities (Figure 1).[2b,5] The stereochemistry of members within this series of lignans is known to significantly affect biological activity; as an example, Ca^{2+} blocking action is observed for trachelogenin, but not for its stereoisomer, epitrachelogenin.[2] Thus, a method is required for the stereoselective synthesis of both *cis*- and *trans*-isomers of α-hydroxy-α,*β*-dibenzyl-*γ*-butyrolactones. However, no report on the stereoselective synthesis of this series of lignans is known. In connection with our efforts in search of new compounds having interesting biological activities from lignans, we have been interested in the synthesis of this series of compounds.[6] We wish to report herein a full account of our effort to the first stereoselective synthesis of *cis*- and *trans*-isomers of α-hydroxy-α,*β*-dibenzyl-*γ*-butyrolactone lignans based on an electrophilic hydroxylation of the metal enolates of α-benzyl-*γ*-butyrolactone derivatives.[7]



1 **2**

a:R^1=3,4-(OMe)$_2$; R^2=3-OMe,4-OH; E=OH
b:R^1=R^2=3-OMe,4-OH; E=OH
c:R^1=3,4-OCH$_2$O; R^2=3,4-(OMe)$_2$; E=OH
d:R^1=3,4-(OMe)$_2$; R^2=3,4-OCH$_2$O; E=OH
e:R^1=3,4,5-(OMe)$_3$; R^2=3,4-OCH$_2$O; E=OH
f:R^1=3,4-(OMe)$_2$; R^2=3-OMe,4-OCH$_2$Ph; E=OH
g:R^1=3,4,5-(OMe)$_3$; R^2=H; E=OH
h:R^1=3,4-(OMe)$_2$; R^2=3,4-OCH$_2$O; E=D
i:R^1=3,4-(OMe)$_2$; R^2=3,4-OCH$_2$O; E=Me
j:R^1=3,4-(OMe)$_2$; R^2=3,4-OCH$_2$O; E=Et
k:R^1=3,4-(OMe)$_2$; R^2=3,4-OCH$_2$O; E=CH$_2$Ph
l:R^1=3,4-(OMe)$_2$; R^2=3,4-OCH$_2$O; E=H
m:R^1=3,4,5-(OMe)$_3$; R^2=3,4-OCH$_2$O; E=H
n:R^1=3,4-(OMe)$_2$; R^2=3-OMe,4-OCH$_2$Ph; E=H
o:R^1=3,4,5-(OMe)$_3$; R^2=H; E=H

Figure 1.

Results and Discussion

Synthetic Strategy and MO Calculations of the Transition Structures. The most convenient and efficient method for the synthesis of α-hydroxy-α,*β*-dibenzyl-*γ*-butyrolactones **1a**−**g** and **2a**−**g** would involve the reaction of the metal enolates of the α,*β*-dibenzyl-*γ*-butyrolactones **1l**−**o** and **2l**−**o** with an oxygen electrophile (Scheme 1).

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⊗ Abstract published in *Advance ACS Abstracts*, September 1, 1996.

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S0022-3263(96)00193-4 CCC: $12.00

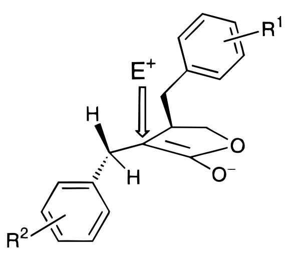
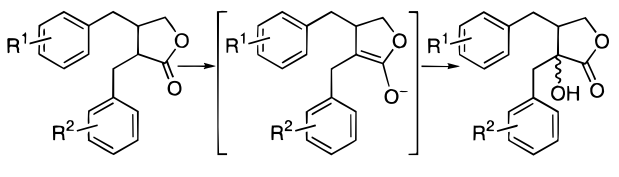


Figure 2.

Scheme 1



1l-o or **2l-o** **1d-g** or **2d-g**

Several reports on the stereoselective alkylation of the metal enolates of γ- and δ-lactones have appeared in the literature. It is well recognized that an electrophilic attack on the enolates of β-substituted γ-butyrolactones is controlled exclusively by the β-substituent, leading to the *trans* addition products.[8] On the other hand, Koga and Tomioka reported the reverse diastereofacial differentiation in the alkylation of the enolates of α,β-disubstituted δ-valerolactones; the facial preference is markedly affected by the exo-allylic substituent, due to the 1,3-allylic strain, only when the exo-allylic substituent is much bulkier than the β-substituent.[9] We envisaged that electrophilic attack on the metal enolates of **1l−o** would take place predominantly from the sterically less hindered upper face in spite of the presence of the β-substituent, due to the shielding effect of the phenyl moiety of the α-benzyl group induced by the 1,3-allylic strain (Figure 2).

In order to evaluate our working hypothesis, we carried out the MO calculations of the transition structures in the electrophilic addition of methyl iodide to the enolate of **1l−o** by using MNDO program for MOPAC. To simplify the calculations, $-O^- Li^+$ was treated as $-O^-$ and the substituted phenyl groups as nonsubstituted phenyl ones. The transition structure in the electrophilic attack from the upper face (**A**) is estimated to be more stable by 2.82 kcal/mol than that from the lower face (**B**) (Figure 3). This result indicates that the electrophilic addition to the enolate of **1l−o** would give **1d−k** in over 98% diastereoexcess (de).[10]

On the other hand, the above results indicate that the stereoselective synthesis of the *cis*-isomer of α-substituted α,β-dibenzyl-γ-butyrolactone **2a−k** by an electrophilic addition to the enolate of **1l−o** is quite difficult. Thus, an alternative approach as shown in Scheme 2 was examined by MO calculations in the same manner, and it was revealed that the transition structure **A** is more stable by 3.28 kcal/mol than **B** (Figure 4); the diastereoexcess of the product could be estimated to be over 99%.[7b]

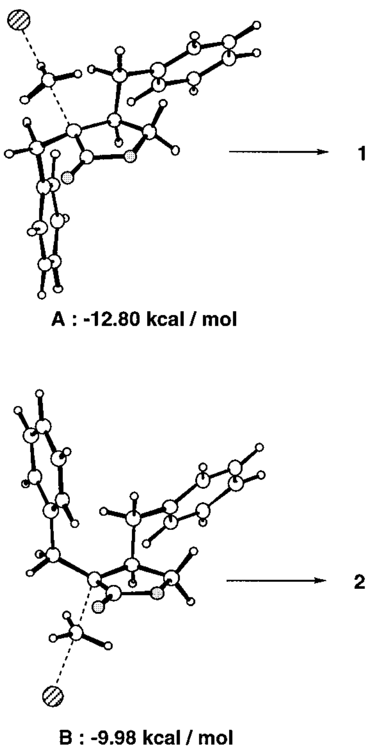
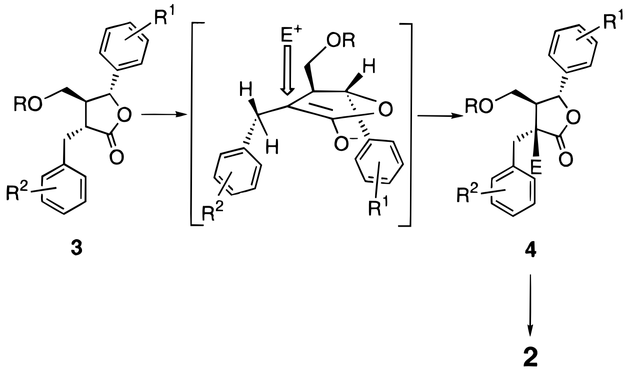


Figure 3.

Scheme 2



Preparation of the γ-Butyrolactones 1l−o, 2l, and 3. Our study began with the preparation of γ-butyrolactones **1l−o**, **2l**, and **3**. The α,β-dibenzyl-γ-butyrolactones **1l−o** and **2l** were prepared from the 4-(substituted benzyl)-γ-butyrolactone **5** obtained by the methods previously reported (Scheme 3).[11] The reaction of the lithium enolate of **5** with the substituted benzyl bromide afforded the *trans*-γ-butyrolactone **1l−o** stereospecifically. The *cis*-γ-butyrolactone **2l** was also synthesized stereospecificially by treating the lithium enolate of **5a** with substituted benzaldehyde to give the aldol product **6**. Acetylation of **6**, followed by treatment with NaH gave the (*E*)-α-benzylidene-γ-butyrolactone **7** as a sole product. Hydrogenation of **7** using 10% Pd on charcoal furnished **2l** exclusively.

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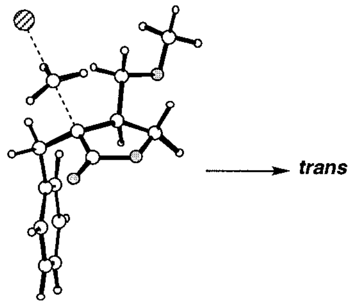
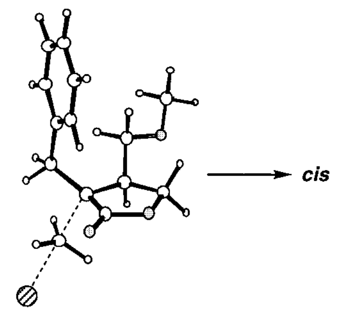
(9) (a) Tomioka, K.; Kawasaki, H.; Koga, K. *Tetrahedron Lett.* **1985**, *26*, 3027. (b) Tomioka, K.; Yasuda, K.; Kawasaki, H.; Koga, K. *Tetrahedron Lett.* **1986**, *27*, 3247. (c) Tomioka, K.; Kawasaki, H.; Yasuda, K.; Koga, K. *J. Am. Chem. Soc.* **1988**, *110*, 3597.

(10) Similar results were obtained when we calculated the heats of formation of the transition structure in the electrophilic addition of methyl iodide to the enolates of dibenzyl lactone using the AM1 or PM3 program.

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



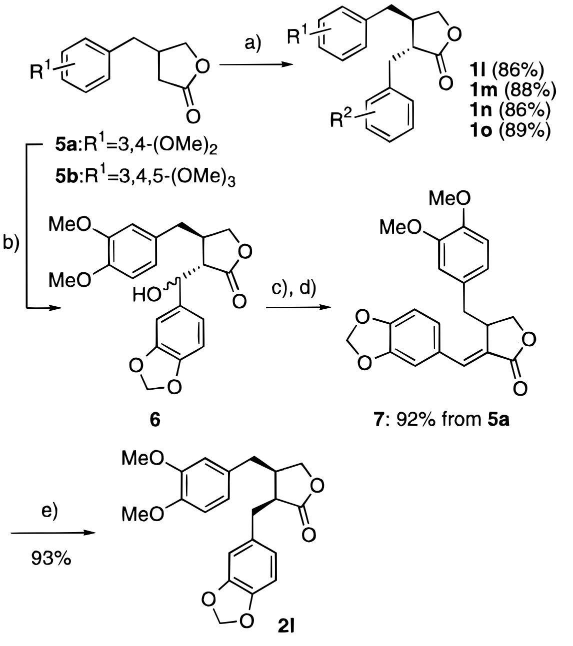
A : -79.84 kcal / mol



B : -76.56 kcal / mol

Figure 4.

Scheme 3



a) LDA, substituted benzylbromide/THF; b) LDA, 3,4-methylenedioxybenzaldehyde/THF; c) Ac$_2$O, Et$_3$N, DMAP/THF; d) NaH/THF; e) H$_2$, Pd-C/THF-MeOH

On the other hand, the γ-butyrolactone **3**, which is required for the synthesis of *cis*-α-substituted α,β-dibenzyl-γ-butyrolactone **2a**−**k**, was prepared starting from the *O*-silylated cyanohydrin **8** (Scheme 4). The conjugate addition of the lithium enolate of **8** to 2(5*H*)-furanone at −78 °C followed by trapping the resulting enolate with 3,4-(methylenedioxy)benzyl bromide gave **9**. Without isolation of **9**, the resulting mixture was treated with tetrabutylammonium fluoride to afford the *trans*-γ-butyrolactone **10**. Reduction of the carbonyl group of **10** with L-Selectride occurred stereospecifically to give only the alcohol **11**; the hydride attacks predominantly from the sterically less hindered site (Figure 5).[12] Treatment of **11** with NaH in DMF afforded **12**. The structure of **12a** was unambiguously determined by X-ray crystallographic analysis; epimerization at the α-carbon of **12** was found to take place completely during the rearrangement. The primary hydroxyl group of **12** was protected by MOM group to afford the desired disubstituted α-benzyl-γ-butyrolactone **3**.

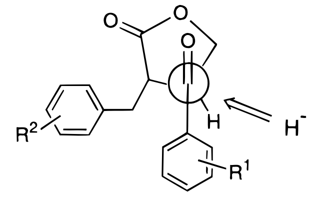
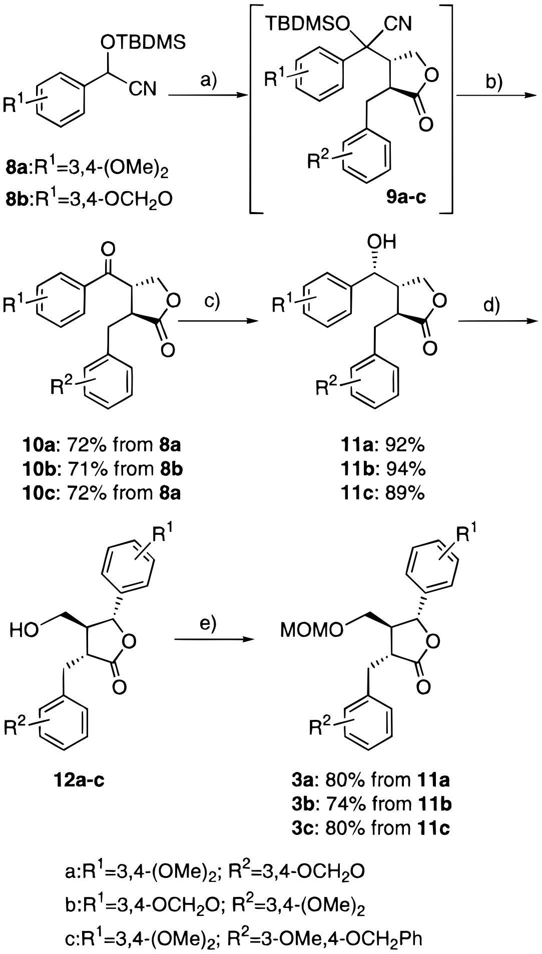


Figure 5.

Scheme 4



a) LDA, 2(5H)-furanone, substituted benzylbromide/THF
b) n-Bu$_4$NF /CH$_2$Cl$_2$ c) L-Selectride/THF d) NaH/DMF
e) MOMCl, i-Pr$_2$NEt/DMF

Synthesis of *trans*-α-Hydroxy-α,β-dibenzyl-γ-butyrolactones. We first evaluated the diastereoselectivity in the electrophilic attack on the metal enolate of **1l** and **2l** by using methyl iodide (MeI) as an electrophile. The potassium enolate generated by the reaction of *trans*-α,β-dibenzyl-γ-butyrolactone **1l** with potassium bis(tri-

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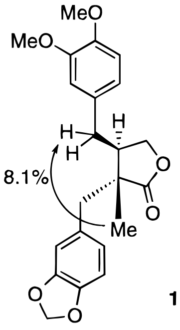
(12) Ogiku, T.; Yoshida, S.; Takahashi, M.; Kuroda, T.; Ohmizu, H.; Iwasaki, T. *Tetrahedron Lett.* **1992**, *33*, 4473; *33*, 4477.

Table 1. Reaction of the Metal Enolates of 1l−o and 2l with Electrophiles

$$\mathbf{1l\text{-}o} \text{ or } \mathbf{2l} \xrightarrow[\text{2) electrophile}]{\text{1) base}} \mathbf{1d\text{-}k} + \mathbf{2d\text{-}k}$$

		reaction conditions		product		
entry	substrate	base (electrophile)	additive (2 equiv)	E	% yield[b] (**1d−k** + **2d−k**)	selectivity (**1d−k**/**2d−k**)
1	**1l**	KHMDS (MeI)	none	Me	94	99/1[d]
2	**2l**	KHMDS (MeI)	none	Me	91	99/1[d]
3	**1l**	KHMDS (D_2O)	none	D	90	94/6[c]
4	**1l**	KHMDS (EtI)	none	Et	90	98/2[d]
5	**1l**	KHMDS (BnBr)	none	Bn	90	67/33[d]
6	**1l**	KHMDS (MoOPH)	none	OH	81	61/39[d]
7	**1l**	LDA (MoOPH)	none	OH	61	62/38[d]
8	**1l**	LiHMDS (MoOPH)	none	OH	42	50/50[d]
9	**1l**	NaHMDS (MoOPH)	none	OH	40	53/47[d]
10	**1l**	KHMDS (MoOPH)	HMPA	OH	80	47/53[d]
11	**1l**	KHMDS (MoOPH)	TMEDA	OH	81	51/49[d]
12	**1l**	KHMDS (MoOPH)	diglyme	OH	84	55/45[d]
13	**1l**	KHMDS (MoOPH)	18-crown-6	OH	94	82/18[d]
14[f]	**1l**	KHMDS (MoOPH)	18-crown-6	OH	94	86/14[e]
15[f]	**1m**	KHMDS (MoOPH)	18-crown-6	OH	91	83/17[e]
16[f]	**1n**	KHMDS (MoOPH)	18-crown-6	OH	93	82/18[e]
17[f]	**1o**	KHMDS (MoOPH)	18-crown-6	OH	94	83/17[e]

[a] The reaction was carried out in THF at −78 °C. [b] Isolated yield. [c] The ratio was determined by ^{1}H NMR. [d] The ratio was determined by HPLC (CAPCELL PAK C_{18}). [e] The ratio was determined by isolated yield of each isomers. [f] The reaction was carried out at −100 °C.



1i

Figure 6.

methylsilyl)amide (KHMDS) in THF at −78 °C was treated with 3 mol equiv of MeI to afford **1i** (Figure 6)[13] and **2i** in a ratio of >99:1 (94% yield) (entry 1 in Table 1): the ratio determined from HPLC. Furthermore, the potassium enolate generated from **2l** gave almost the same diastereoselectively (entry 2). These results indicate that the phenyl moiety of the α-benzyl group in the metal enolate of **1l** and **2l** is sterically bulky enough to allow the β-face entry of an electrophile.

In order to evaluate the effect of other electrophiles on the diastereoselectivity, the enolate was treated with D_2O,[14,15] ethyl iodide (EtI), and benzyl bromide (BnBr). Deuteriation and ethylation of **1l** similarly proceeded in a stereoselective manner to give **1h**, **1j** as the major product, respectively (entries 3, 4). However, benzylation of **1l** did not proceed so diastereoselectively, resulting in a 67:33 ratio of **1k** and **2k** in 90% yield (entry 5). The results indicate that an increase in bulkiness of the electrophile reduces the diastereoselectivity of the reaction.

We next examined the hydroxylation[16] of **1l−o** prior to synthesizing (±)-trachelogenin and related compounds. The potassium enolate, generated by treatment of **1l** with KHMDS, was treated with oxodiperoxymolybdenum(pyridine)(hexamethylphosphorictriamide) (MoOPH).[17] In this reaction, the *trans*-isomer **1d** was obtained as the major product, but the diastereoselectivity was rather low (entry 6 in Table 1). In order to improve the diastereoselectivity, we examined the reaction by using a base other than KHMDS (entries 7−9). However, the diastereoselectivity was not improved in any case, and the yields were lower. We thought that the presence of the counter cation in the metal enolate might have slightly changed the transition structure of the reaction from that used in the evaluation of our working hypothesis by MO calculation. This might dramatically alter the expected diastereoselectivity in the case of a more bulky electrophile such as MoOPH. In order to negate the prominent role of the counter cation on the transition structure, the reaction was examined in the presence of additives such as tetramethylethylenediamine (TMEDA), hexamethylphosphorictriamide (HMPA), diglyme, and 18-crown-6. We first examined the use of HMPA and TMEDA, the representative nitrogen-containing cation-trapping reagents. However, the diastereoselectivity was not improved at all (entries 10, 11). We next examined the ether type cation trapping reagents, diglyme and 18-crown-6. Although no improvement in the diastereoselectivity and yield was observed in the case of diglyme (entry 12), the use of 18-crown-6 resulted in a remarkable improvement in both the diastereoselectivity and yield (entry 13). Furthermore the diastereoselectivity increased to be 86:14 when the reaction was carried out at −100 °C (entry 14). Almost the same result was obtained

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[13] The structure of **1i** was unambiguously determined by X-ray crystallographic analysis and 400 MHz ^{1}H NMR (NOE).

[14] It was suggested in the literature that the deuteriation proceed by a mechanism different from that of the alkylation. This might be the reason why the stereoselectivity in the case of deuteriation did not depend on the order of bulkiness of the electrophiles.[15]

[15] Deuteriation probably takes place first on oxygen and the stereochemistry-determining step is the second deuteriation on carbon; Fleming, I.; Lewis, J. J. *J. Chem. Soc., Chem. Commun.* **1985**, 149.

[16] Brown *et al.* reported the hydroxylation of the enolate of **1l−o** with molecular hydrogen. However, the diastereoselectivity was not observed in this reaction, see ref 2c.

[17] Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188.

[18] The NMR spectra of the products (**1a**, **2c**) obtained here were completely consistent with those of (±)-trachelogenin and (±)-guayadequiol reported in refs 1−3.

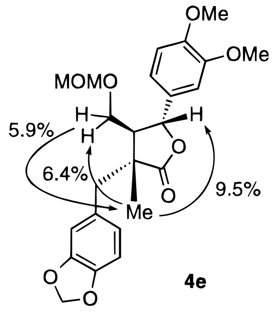


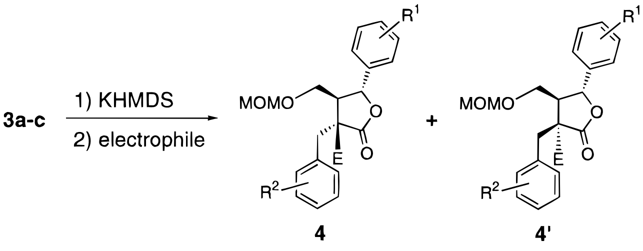
Figure 7.

Scheme 5

$$\mathbf{1n} \xrightarrow[76\%]{a)} \mathbf{1f} \xrightarrow[96\%]{b)} (\pm)\text{-trachelogenin } (\mathbf{1a})$$

a) KHMDS, MoOPH, 18-crown-6/THF
b) H_2, Pd-C/THF-MeOH

Table 2. Reaction of the Metal Enolates of 3a–c with Electrophiles



a: R^1=3,4-(OMe)$_2$; R^2=3,4-OCH$_2$O; E=OH
b: R^1=3,4-OCH$_2$O; R^2=3,4-(OMe)$_2$; E=OH
c: R^1=3,4-(OMe)$_2$; R^2=3-OMe,4-OCH$_2$Ph; E=OH
d: R^1=3,4-(OMe)$_2$; R^2=3,4-OCH$_2$O; E=D
e: R^1=3,4-(OMe)$_2$; R^2=3,4-OCH$_2$O; E=Me
f: R^1=3,4-(OMe)$_2$; R^2=3,4-OCH$_2$O; E=Et

entry	substrate	electrophile	E	% yield[b] (**4**+**4′**)	selectivity (**4**/**4′**)
1	**3a**	MeI	Me	87	>99/1[d]
2	**3a**	D_2O	D	92	>99/1[c]
3	**3a**	EtI	Et	89	>99/1[d]
4	**3a**	MoOPH	OH	89	>99/1[d]
5	**3b**	MoOPH	OH	83	>99/1[d]
6	**3c**	MoOPH	OH	81	>99/1[d]

[a] The reaction was carried out in THF at −78 °C using KHMDS as a base. [b] Isolated yield. [c] The ratio was determined by ^{1}H NMR after transformation into **2**. [d] The ratio was determined by HPLC (CAPCELL PAK C_{18}) after transformation into **2**.

in the case of **1n**, the precursor of (±)-trachelogenin (**1f**) (entry 16). Hydrogenolysis of **1f** afforded (±)-trachelogenin (**1a**)[18] in 96% yield. (Scheme 5).

Synthesis of *cis*-α-Hydroxy-α,β-dibenzyl-γ-butyrolactones. In order to further evaluate our working hypotheses (**3** to **4** in Scheme 2), we similarly examined electrophilic additions to the metal enolates of γ-butyrolactones **3** by using D_2O, MeI and EtI as electrophiles. The potassium enolate generated by reaction of **3a** with KHMDS in THF at −78 °C was treated with MeI to furnish **4e** (Figure 7)[19] and its stereoisomer **4′e** in 87% yield, in a ratio of >99:1 by the HPLC analysis (entry 1 in Table 2). We next attempted to introduce a variety of electrophiles into the metal enolate of **3** prior to synthesizing (±)-guayadequiol **2c** and its derivatives. Deuteriation and ethylation of **3a** using D_2O and EtI, respectively, as electrophiles was found to proceed smoothly with a high level of diastereoselectivity to afford **4d**, **4f** as the sole product (entries 2, 3). Furthermore, hydroxylation of **3** also proceeded with high diastereoselectivity to give **4a**–**c**[20] exclusively (Figure 8, entries 4–6). The results are summarized in Table 2.

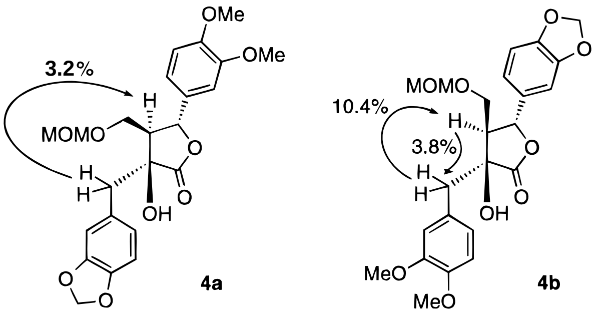


Figure 8.

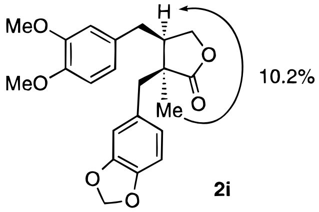
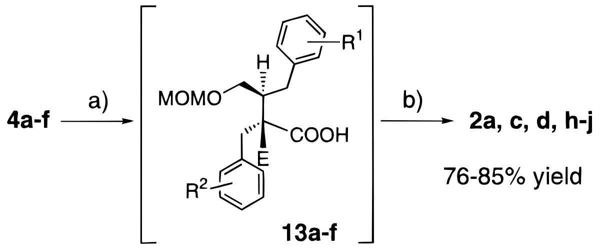


Figure 9.

Scheme 6



a) H_2, Pd-C, conc.H_2SO_4/AcOH b) conc.H_2SO_4/AcOH-H_2O-THF

We next investigated the conversion of **4a**–**f** into the desired *cis*-dibenzyl lactones **2a**, **2c**, **2d**, **2h**–**j** (Scheme 6). In order to cleave the lactone ether bond, hydrogenolysis of **4a** was examined in several solvents using 10% Pd on charcoal as a catalyst. In THF or THF–MeOH, the reaction proceeded very sluggishly; even after 24 h at room temperature, little product (**13a**) was obtained. However, the reaction proceeded smoothly to **13a** in AcOH containing a catalytic amount of concd H_2SO_4. Without isolation of **13a**, the mixture was treated under aqueous acidic conditions to afford the desired product **2d** in 85% yield. Other compounds **2a**, **2c**, **2h**, **2i** (Figure 9)[21] and **2j** were also obtained in moderate to good yield by the same procedure described above.

This method was applied to the synthesis of (±)-guayadequiol (**2c**), a representative example of the naturally occurring lignans. Hydroxylation of the metal enolate of **3b** with MoOPH proceeded in a highly diastereoselective manner to afford the *trans*-product **4b** (Figure 8, entry 6 in Table 2).[22] This was nicely trans-

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(19) The structure of **4e** was determined by 400 MHz ^{1}H NMR.

(20) The structure of **4a** was determined by 200 MHz ^{1}H NMR.

(21) The structure of **2i** was unambiguously determined by X-ray crystallographic analysis and 400 MHz ^{1}H NMR (NOE).

(22) The structure of **4b** was determined by 200 MHz ^{1}H NMR.

formed into (±)-guayadequiol (**2c**)[18] using the same procedure described above.

Conclusion

We present here a highly stereoselective electrophilic addition reaction to the metal enolate of the β-substituted α-benzyl-γ-butyrolactone derivatives **1l**−**o** and **3**. The stereoselectivity observed in this reaction presumably originates from the conformational rigidity of the metal enolate of **1l**−**o** and **3** induced by 1,3-allylic strain. Using this reaction, the first stereoselective synthesis of both *cis*- and *trans*-isomers of α-substituted α,β-dibenzyl-γ-butyrolactones was accomplished. This method should find wide application in the stereoselective synthesis of a variety of *cis*- and *trans*-isomers of α-substituted α,β-dibenzyl-γ-butyrolactone lignans having intriguing biological activities.

Experimental Section

General Considerations. All melting points are uncorrected. HPLC analyses were performed with SHISEIDO CAPCELLPAC C18 (SG 120, S-5 μm, 4.6 × 150 mm) and a flow rate of 0.5 mL/min.

Computational Methods. Semiempirical molecular orbital calculations were carried out using MNDO Hamiltonian implemented in MOPAC 5.0.[23] Conformational analyses were previously done using the command SEARCH in SYBYL[24] with TRIPOS force field. All structures were refined using the keyword PRESCISE. Transition structures were calculated by using bond lengths of I−C(Me) and C(Me)−Cα as reaction coordinates, using product structures as starting structures in calculations for convenience. The structures were further optimized with the keyword NLLSQ, and then vibrational analyses were done with the keyword FORCE, to verify the transition structures.

Synthesis of β-Benzyl-γ-butyrolactones 5. Typical Procedure. To a solution of t-BuOK (67.6 g, 0.602 mol) in t-BuOH (600 mL) were added veratraldehyde (100 g, 0.602 mol) and dimethyl succinate (80.9 mL, 0.602 mol), keeping the temperature 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 and brine and dried over $MgSO_4$. Evaporation of the solvent provided the veratrylidene half ester as a yellowish solid, which was collected by filtration and washed with Et_2O (94.0 g, 56%). The yellowish solid (75.0 g, 0.267 mol) was suspended in MeOH (800 mL) and stirred under nitrogen. 10% Pd on charcoal (4.0 g) was added, 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 filtration and washed with 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 mL of EtOH) to a suspension of the veratryl half ester in EtOH (600 mL) until basic to phenolphthalein. Powdered anhydrous $CaCl_2$ (100 g, 0.90 mol) was dissolved in anhydrous EtOH (800 mL) and cooled to −10 °C. To this was added a solution of $NaBH_4$ (70.0 g, 1.85 mol) in EtOH (1800 mL) over 1 h at −10 °C, the potassium salt in EtOH was added to the borohydride solution over 1 h at −78 °C, and the mixture was stirred for 12 h at room temperature. The mixture was concentrated, and the residue was dissolved in water and $CHCl_3$, acidified by concd HCl to pH = 1−2, and refluxed for 30 min. The organic layer of the cooled reaction mixture was separated, washed with water and brine, and dried over $MgSO_4$. Evaporation of the solvent left a yellowish oil that was purified by silica gel column chromatography using hexane/AcOEt (1:1) as an eluent to afford **5a** (58.2 g, 90%) as a colorless oil.

4-(3,4-Dimethoxybenzyl)-γ-butyrolactone (5a): 47% yield from veratraldehyde; IR (film) 1778 cm^{-1}; ^{1}H NMR (δ in $CDCl_3$); 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* (relative intensity, %): 236 (M^+, 57), 151 (100). Anal. Calcd for $C_{13}H_{16}O_4$: C, 68.10; H, 5.99. Found: C, 67.92; H, 5.98.

(3*R,4*R**)-3-[3,4-(Methylenedioxy)benzyl]-4-(3,4-dimethoxybenzyl)-γ-butyrolactone (1l).** LDA (60.4 mmol) was prepared in 60 mL of THF by the normal method.[6d] To the solution cooled to −78 °C was added dropwise **5a** (11.9 g, 50.3 mmol) in THF (30 mL) while maintaining the same temperature. After 20 min, 3,4-(methylenedioxy)benzyl bromide (10.8 g, 50.3 mmol) in THF (30 mL) was added to the mixture, which was stirred for an additional 3 h at −78 °C. The mixture was quenched with saturated aqueous ammonium chloride, the organic layer separated, and the aqueous layer extracted with AcOEt. The combined organic layers were washed with water and brine and dried over $MgSO_4$. Evaporation of the solvent provided the crude product as a solid, which was collected by filtration and washed with Et_2O to afford **1l** (16.0 g, 86%): mp 107−8 °C (AcOEt−hexane); IR (KBr) 1767 cm^{-1}; ^{1}H NMR (δ in $CDCl_3$) 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), 3.81−3.98 (m, 1H), 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* (relative intensity, %): 370 (M^+, 50), 151 (73), 135 (100). Anal. Calcd for $C_{21}H_{22}O_6$: C, 68.10; H, 5.99. Found: C, 67.92; H, 5.98.

Synthesis of *cis*-α,β-Dibenzyl-γ-butyrolactones (2l). Reaction of LDA (36.0 mmol) in 50 mL of THF and **5a** (7.08 g, 30 mmol) in THF (20 mL) was carried out as described for **1l**. After 20 min, further reaction with 3,4-(methylenedioxy)benzaldehyde (4.50 g, 30 mmol) in THF (10 mL) for 1 h at −78 °C followed by workup as described for **1l** provided crude **6** as an oil. Without isolation, **6** was treated with acetic anhydride (3.68 mL, 39.0 mmol), triethylamine (5.44 mL, 39.0 mmol), and (dimethylamino)pyridine (0.37 g, 3 mmol) in THF (100 mL) at room temperature for 5 h. The reaction mixture was poured into water, and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with water and brine and dried over $MgSO_4$. Evaporation of the solvent provided the acetylated product after purification by silica gel column chromatography using $CHCl_3$/AcOEt (20:1) as an eluent. The acetate was dissolved in THF (100 mL), and sodium hydride (2.40 g, 60 mmol) was added portionwise to the mixture at 0 °C. The mixture was stirred at room temperature for 12 h, quenched with water, and acidified to pH = 1−2 with 2 N HCl. The aqueous layer was extracted with AcOEt, and the combined organic layers were washed with water and brine and dried over $MgSO_4$. Evaporation of the solvent provided the exo-olefin **7** as a solid, which was collected by filtration and washed with Et_2O (10.1 g, 92%). A sample of **7** (8.88 g, 24.1 mmol) was dissolved in a mixture of THF (80 mL) and MeOH (40 mL), and 10% Pd/C (500 mg) catalyst was added. The mixture was stirred under H_2 (1 atm, rt) for 4 h followed by filtration and evaporation to give *cis*-dibenzyl lactone **2l** (8.31 g, 93%) as the sole product.

(3*E*)-[3,4-(Methylenedioxy)benzylidene]-4-(3,4-dimethoxybenzyl)-γ-butyrolactone (7): mp 95−6 °C (AcOEt−hexane); IR (KBr) 1738 cm^{-1}; ^{1}H NMR (δ in $CDCl_3$) 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* (relative intensity, %): 368 (M^+, 25), 217 (8), 151 (100). Anal. Calcd for $C_{21}H_{20}O_6$: C, 68.47; H, 5.47. Found: C, 68.44; H, 5.29.

(3*S,4*R**)-3-[3,4-(Methylenedioxy)benzyl]-4-(3,4-dimethoxybenzyl)-γ-butyrolactone (2l):** mp 103−4 °C (AcOEt−hexane); IR (KBr) 1771 cm^{-1}; ^{1}H NMR (δ in $CDCl_3$) 2.32 (dd, 1H, J = 12.3, 13.3 Hz), 2.59−2.78 (m, 1H), 2.76 (dd,

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[23] MOPAC Ver. 5, J. J. P. Stewart, QCPE No. 455; Revised as Ver. 5.01 by T. Hirano, for UNIX machines, *JCPE Newletter* **1989**, *1(2)*, 36.

[24] TRIPOS, Inc., 1699 S. Hanley Road, St. Louis, MO 63144-2913.

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, 6H), 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* (relative intensity, %): 370 (M$^+$, 60), 151 (59), 135 (100). Anal. Calcd for $C_{21}H_{22}O_6$: C, 68.10; H, 5.99. Found: C, 68.04; H, 5.79.

Deuteriation of the Metal Enolate of 1l. A solution of **1l** (430 mg, 1.16 mmol) in 5 mL of THF was added to the solution of KHMDS (488 mg, 2.32 mmol) in 8 mL of THF at −78 °C, and the mixture was stirred for 30 min at the same temperature. To the mixture was added dropwise D_2O (1.0 mL, large excess), and it was stirred for 1 h. The organic layer was separated and dried over $MgSO_4$. Evaporation of the solvent provided a mixture of **1h** and **2h**, which was separated by silica gel column chromatography using hexane/$CHCl_3$/AcOEt (10:10:1) as the eluent; the ratio of isomers was determined by ^{1}H NMR analysis.

(3*R,4*R**)-3-Deuterio-3-[3,4-(methylenedioxy)benzyl]-4-(3,4-dimethoxybenzyl)-γ-butyrolactone (1h):** mp 98−9 °C (AcOEt−hexane); IR (KBr) 1767 cm^{-1}; ^{1}H NMR (δ in $CDCl_3$) 2.39−2.68 (m, 3H), 2.74 (d, 1H, J = 14.2 Hz), 2.97 (d, 1H, J = 14.1 Hz), 3.83 (s, 3H), 3.86 (s, 3H), 3.82−3.93 (m, 1H), 4.15 (dd, 1H, J = 7.1, 9.5 Hz), 5.91−5.99 (m, 2H), 6.48 (d, 1H, J = 1.9 Hz), 6.51−6.59 (m, 1H), 6.60 (s, 2H), 6.68−6.84 (m, 2H); MS *m/z* (relative intensity, %): 371 (M$^+$, 44), 151 (73), 135 (100).

(3*R,4*S**)-3-Deuterio-3-[3,4-(methylenedioxy)benzyl]-4-(3,4-dimethoxybenzyl)-γ-butyrolactone (2h):** mp 102−3 °C (AcOEt−hexane); IR (KBr) 1774 cm^{-1}; ^{1}H NMR (δ in $CDCl_3$) 2.32 (dd, 1H, J = 12.3, 13.3 Hz), 2.59−3.12 (m, 3H), 3.22 (d, 1H, J = 14.9 Hz), 3.84 (s, 3H), 3.85 (s, 3H), 3.96−4.12 (m, 2H), 5.96 (s, 2H), 6.53 (d, 1H, J = 1.9 Hz), 6.61 (dd, 1H, J = 1.9, 8.1 Hz), 6.71−6.87 (m, 4H); MS *m/z* (relative intensity, %); 371 (M$^+$, 89), 151 (69), 135 (100).

Alkylation of the Metal Enolate of 1l−o, 2l. Typical Procedure. The potassium enolate of **1l** (370 mg, 1.00 mmol) was prepared from KHMDS (420 mg, 2.00 mmol) as described above for **1h** and **2h**. To the mixture was added dropwise MeI (0.187 mL, 3.00 mmol) in 8 mL of THF. After 2 h, 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 layers were washed with saturated aqueous sodium thiosulfate, water, and brine and dried over $MgSO_4$. Evaporation of the solvent provided **1i** as the sole product, which was purified by silica gel column chromatography using hexane/$CHCl_3$/AcOEt (10:10:1) as the eluent. The diastereoselectivity was determined by HPLC with 45:55 CH_3CN-H_2O as the mobile phase.

(3*R,4*R**)-3-Methyl-3-[3,4-(methylenedioxy)benzyl]-4-(3,4-dimethoxybenzyl)-γ-butyrolactone (1i):** mp 96−7 °C (AcOEt−hexane); IR (KBr) 1777, 1517, cm^{-1}; 400 MHz ^{1}H NMR (δ in $CDCl_3$), 1.25 (m, 3H), 2.36 (dd, 1H, J = 11.0, 13.4 Hz), 2.48−2.68 (m, 1H), 2.64 (d, 1H, J = 14.0 Hz), 2.69 (dd, 1H, J = 4.0, 13.4 Hz), 3.15 (d, 1H, J = 14.0 Hz), 3.83 (dd, 1H, J = 9.1, 10.2 Hz), 3.85 (s, 3H), 3.86 (s, 3H), 3.98 (dd, 1H, J = 7.8, 9.1 Hz), 5.93 (s, 2H), 6.55 (d, 1H, J = 2.2 Hz), 6.60 (dd, 1H, J = 2.1, 8.3 Hz), 6.64 (dd, 1H, J = 2.1, 8.3 Hz), 6.70 (d, 1H, J = 1.6 Hz), 6.74 (d, 1H, J = 7.8 Hz), 6.77 (d, 1H, J = 8.3 Hz); MS *m/z* (relative intensity, %); 384 (M$^+$, 27), 151 (17), 135 (100). Anal. Calcd for $C_{22}H_{24}O_6$: C, 68.74; H, 6.29. Found: C, 68.56; H, 6.12.

Ethylation and benzylation of **1l** were conducted in the same manner described above.

(3*R,4*R**)-3-Ethyl-3-[3,4-(methylenedioxy)benzyl]-4-(3,4-dimethoxybenzyl)-γ-butyrolactone (1j):** mp 138−9 °C (AcOEt); IR (KBr) 1761 cm^{-1}; ^{1}H NMR (δ in $CDCl_3$), 1.13 (t, 3H, J = 7.4), 1.58−1.91 (m, 2H), 2.31−2.77 (m, 3H), 2.60 (d, 1H, J = 14.1 Hz), 3.24 (d, 1H, J = 14.0 Hz), 3.72−3.99 (m, 2H), 3.85 (s, 6H), 5.93 (s, 2H), 6.48−6.82 (m, 6H); MS *m/z* (relative intensity, %): 400 (M$^+$, 64), 207 (18), 181 (59), 135 (100). Anal. Calcd for $C_{23}H_{26}O_6$: C, 69.33; H, 6.58. Found: C, 69.20; H, 6.32.

(3*R,4*R**)-3-Benzyl-3-[3,4-(methylenedioxy)benzyl]-4-(3,4-dimethoxybenzyl)-γ-butyrolactone (1k):** mp 101−2 °C (AcOEt−hexane); IR (KBr) 1762 cm^{-1}; ^{1}H NMR (δ in $CDCl_3$) 2.50−2.82 (m, 2H), 2.70 (d, 1H, J = 14.1 Hz), 2.86−2.98 (m, 1H), 2.96 (d, 1H, J = 11.9 Hz), 3.04 (d, 1H, J = 13.8 Hz), 3.23 (d, 1H, J = 14.0 Hz), 3.50 (dd, 1H, J = 8.8, 10.6 Hz), 3.74−3.89 (m, 1H), 3.84 (s, 6H), 5.92 (s, 2H), 6.48−6.81 (m, 6H), 7.18−7.43 (m, 5H); MS *m/z* (relative intensity, %): 460 (M$^+$, 17), 151 (30), 135 (100). Anal. Calcd for $C_{28}H_{28}O_6$: C, 73.03; H, 6.13. Found: C, 72.98; H, 6.32.

(3*S,4*R**)-3-Benzyl-3-[3,4-(methylenedioxy)benzyl]-4-(3,4-dimethoxybenzyl)-γ-butyrolactone (2k):** mp 122−3 °C (AcOEt−hexane); IR (KBr) 1761 cm^{-1}; ^{1}H NMR (δ in $CDCl_3$) 2.43−2.78 (m, 2H), 2.74 (d, 1H, J = 13.8 Hz), 2.82−3.08 (m, 3H), 3.33 (d, 1H, J = 13.8 Hz), 3.60 (dd, 1H, J = 8.6, 10.6 Hz), 3.74−3.89 (m, 1H), 3.81 (s, 3H), 3.84 (s, 3H), 5.97 (s, 2H), 6.44−6.83 (m, 6H), 7.13−7.42 (m, 5H); MS *m/z* (relative intensity, %); 460 (M$^+$, 29), 338 (43), 151 (45), 135 (100). Anal. Calcd for $C_{28}H_{28}O_6$: C, 73.03; H, 6.13. Found: C, 73.14; H, 6.22.

Hydroxylation of the Metal Enolate of 1l−o. General Procedure. A solution of **1l−o** (1.00 mmol) in 8 mL of THF was added to a solution of the base (2.00 mmol) in 8 mL of THF at −78 °C and additive (2.00 mmol) in 3 mL of THF if it is necessary. The mixture was stirred for 30 min at the same temperature. To the mixture was added MoOPH (533 mg, 1.50 mmol) in one portion, and it was stirred for 1−2 h. The mixture was quenched by addition of saturated aqueous sodium sulfate (5 mL). The organic layer was separated, and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with 2 N HCl, water, and brine and dried over $MgSO_4$. Evaporation of the solvent provided a crude mixture, which was purified by silica gel column chromatography using hexane/$CHCl_3$/AcOEt (5:5:3) as the eluent to afford **1d−g** and **2d−g** as colorless crystalline solids. The yield and the ratio of each isomer are shown in Table 1.

(3*S,4*S**)-3-Hydroxy-3-[3,4-(methylenedioxy)benzyl]-4-(3,4-dimethoxybenzyl)-γ-butyrolactone (1d):** mp 153−4 °C (AcOEt); IR (KBr) 3426, 1754 cm^{-1}; ^{1}H NMR (δ in $CDCl_3$) 2.41−2.64 (m, 3H), 2.91 (d, 1H, J = 13.8 Hz), 3.07 (d, 1H, J = 13.8 Hz), 2.90−3.02 (m, 1H), 3.86 (s, 6H), 3.95−4.13 (m, 2H), 5.94 (s, 2H), 6.57−6.85 (m, 6H); MS *m/z* (relative intensity, %): 386 (M$^+$, 17), 151 (13), 135 (100), 77 (6). Anal. Calcd for $C_{21}H_{22}O_7$: C, 65.28; H, 5.74. Found: C, 65.19; H, 5.63.

(3*R,4*S**)-3-Hydroxy-3-[3,4-(methylenedioxy)benzyl]-4-(3,4-dimethoxybenzyl)-γ-butyrolactone (2d):** mp 140−1 °C (AcOEt); IR (KBr) 3520, 1783 cm^{-1}; ^{1}H NMR (δ in $CDCl_3$) 2.64 (dd, 1H, J = 11.3, 13.2 Hz), 2.73 (s, 1H), 2.82−3.06 (m, 3H), 3.13 (dd, 1H, J = 4.0, 13.3 Hz), 3.87 (s, 3H), 3.88 (s, 3H), 3.93 (dd, 1H, J = 10.1, 10.1 Hz), 4.20 (dd, 1H, J = 7.7, 9.1 Hz), 5.96 (s, 2H), 6.62−6.87 (m, 6H); MS *m/z* (relative intensity, %): 386 (M$^+$, 13), 151 (9), 135 (100), 77 (5). Anal. Calcd for $C_{21}H_{22}O_7$: C, 65.28; H, 5.74. Found: C, 65.06: H, 5.54.

(±)-Trachelogenin (1a). *Trans*-lactone **1f** (0.60 g, 1.26 mmol) was dissolved in a mixture of THF (10 mL) and MeOH (10 mL), and 10% Pd/C (100 mg) was added. The mixture was stirred under a hydrogen atmosphere at 25 °C for 6 h. Filtration of the catalyst and evaporation of the solvent left 468 mg (96% yield) of a crude solid. Recrystallization from MeOH furnished pure **1a** as prisms: mp 138−9 °C (MeOH) [lit.[2a] mp 130−140 °C; lit.[2c] (−)-trachelogenin: mp 139.3−140.5 °C (CH_2Cl_2−ether)]; IR (KBr) 3455, 1752 cm^{-1}; ^{1}H NMR (δ in $CDCl_3$) 2.44−2.63 (m, 2H), 2.61 (s, 1H), 2.88−3.07 (m, 1H), 2.93 (d, 1H, J = 13.8 Hz), 3.11 (d, 1H, J = 13.7 Hz), 3.848 (s, 3H), 3.853 (s, 3H), 3.86 (s, 3H), 3.93−4.13 (m, 2H), 5.59 (s, 1H), 6.58−6.90 (m, 6H); MS *m/z* (relative intensity, %): 388 (M$^+$, 12), 151 (14), 137 (100). Anal. Calcd for $C_{21}H_{24}O_7$: C, 64:94; H, 6.23. Found: C, 64.88: H, 6.39.

Synthesis of Cyanohydrins (8). Compounds **8a** and **8b** were prepared from the substituted benzaldehyde by the reported method.[6e]

(3*R,4*R**)-3-[3,4-(Methylenedioxy)benzyl]-4-(3,4-dimethoxybenzoyl)-γ-butyrolactone (10a).** LDA (0.35 mol) in THF (400 mL) was prepared by the normal method and cooled to −78 °C. To the solution was added dropwise **8a** (90.0 g, 0.290 mol) in THF (200 mL) under vigorous stirring, followed by successive addition of 2(5*H*)-furanone (20.7 mL, 0.290 mol) in THF (200 mL) and 3,4-(methylenedioxy)benzyl bromide (63.0 g, 0.290 mol) in THF (100 mL) at the same temperature. After 3 h, 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 layers were washed with water and brine and dried over $MgSO_4$. Evaporation of the solvent provided the crude product (**9a**) as an oil. To the solution of the oily product in CH_2Cl_2 (1500 mL) was added 1 M Bu_4NF in THF (293 mL, 0.290 mol) at 0 °C. After 30 min, the solution was washed with water, 10% citric acid, and brine and dried over $MgSO_4$. Evaporation of the solvent afforded a crude product, which was crystallized from MeOH to give **10a** (80.8 g, 72% from **8a**) as the sole product: mp 140−1 °C (AcOEt−acetone): IR (KBr) 1772, 1665 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 2.93 (dd, 1H, J = 7.2, 14.2 Hz), 3.06 (dd, 1H, J = 5.5, 14.2 Hz), 3.42−3.63 (m, 1H), 3.17 (dd, 1H, J = 3.8, 13.2 Hz), 3.92 (s, 3H), 3.96 (s, 3H), 4.01−4.23 (m, 2H), 4.32−4.51 (m, 1H), 5.85 (d, 1H, J = 1.3 Hz), 5.88 (d, 1H, J = 1.4 Hz), 6.49−6.68 (m, 3H), 6.84 (d, 1H, J = 8.4 Hz), 7.23−7.41 (m, 2H); MS m/z (relative intensity, %): 384 (M^+, 37), 192 (100), 165 (61), 135 (35). Anal. Calcd for $C_{21}H_{20}O_7$: C, 65.62; H, 5.24. Found: C, 65.69; H, 5.12.

(3R*,4R*)-3-[3,4-(Methylenedioxy)benzyl]-4-[(αS*)-α-hydroxy-3,4-dimethoxybenzyl]-γ-butyrolactone (11a). To the solution of the ketone **10a** (10.0 g, 26.1 mmol) in THF (150 mL) was added dropwise L-Selectride (1.0 M in THF, 28.6 mL, 28.6 mmol) at −78 °C, and stirring was continued for 5 h at −20 °C. The mixture was quenched by the addition of AcOH (1.73 mL, 28.7 mmol) and concentrated. The residue was diluted with AcOEt (100 mL) and washed with water and brine, and dried over $MgSO_4$. Evaporation of the solvent provided the crude product, which was purified by silica gel column chromatography using $CHCl_3$/acetone (10:1) as the eluent to afford **11a** as the sole diastereomer (9.2 g, 92% yield) as a syrup: IR (KBr) 3500, 1765 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 2.08 (d, 1H, J = 2.7 Hz), 2.50−2.70 (m, 1H), 2.80−3.10 (m, 3H), 3.85 (s, 3H), 3.88 (s, 3H), 3.98 (dd, 2H, J = 1.7, 7.8 Hz), 4.66 (dd, 1H, J = 2.7, 6.4 Hz), 5.85−5.95 (m, 2H), 6.50−6.85 (m, 6H); MS m/z (relative intensity, %): 386 (M^+, 25), 167 (100), 135 (54). Anal. Calcd for $C_{21}H_{22}O_7$: C, 65.28; H, 5.74. Found: C, 65.21; H, 5.63.

(3R*,4S*,5R*)-3-[3,4-(Methylenedioxy)benzyl]-4-[[(methoxymethyl)oxy]methyl]-5-(3,4-dimethoxyphenyl)-γ-butyrolactone (3a). To an ice-cooled solution of **11a** (5.00 g, 13.0 mmol) in DMF (50 mL) was added sodium hydride (544 mg, 13.7 mmol), and the mixture was stirred at the same temperature for 1 h. The mixture was quenched by the addition of 2 N HCl (6.8 mL), and the DMF was removed in vacuo. The residue was extracted with AcOEt, and the combined organic layers were washed with water and brine and dried over $MgSO_4$. Evaporation of the solvent provided the crude product (**12a**), which was not purified but used directly for the synthesis of **3a**. The crude product **12a** (5.00 g, 13.0 mmol) and diisopropylethylamine (2.90 mL, 16.9 mmol) were dissolved in DMF (30 mL), and the solution was ice-cooled. To the mixture was added chloromethyl methyl ether (1.28 mL, 16.9 mmol), and the resulting mixture was stirred for 12 h at room temperature. The mixture was poured into water and extracted with AcOEt. The combined organic layers were washed with water, 10% citric acid, saturated aqueous $NaHCO_3$, and brine and dried over $MgSO_4$. Evaporation of the solvent provided the crude oil, which was purified by silica gel column chromatography using hexane/$CHCl_3$/AcOEt (5:5:3) as the eluent to afford **3a** (4.50 g) in 80% yield: mp 146−7 °C (AcOEt); IR (KBr) 1761 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 2.12−2.40 (m, 1H), 2.96−3.21 (m, 3H), 3.30 (dd, 1H, J = 3.8, 10.3 Hz), 3.34 (s, 3H), 3.44 (dd, 1H, J = 3.7, 10.3 Hz), 3.79 (s, 3H), 3.87 (s, 3H), 4.51 (d, 1H, J = 6.6 Hz), 4.59 (d, 1H, J = 6.6 Hz), 5.15 (d, 1H, J = 9.2 Hz), 5.92 (s, 2H), 6.58 (d, 1H, J = 1.7 Hz), 6.63−6.86 (m, 5H); MS m/z (relative intensity, %): 430 (M^+, 62), 238 (37), 193 (45), 165 (56), 135 (100). Anal. Calcd for $C_{23}H_{26}O_8$: C, 64.18; H, 6.09. Found: C, 64.10; H, 6.04.

(3S*,4S*,5R*)-3-[3,4-(Methylenedioxy)benzyl]-4-(hydroxymethyl)-5-(3,4-dimethoxyphenyl)-γ-butyrolactone (12a). An analytical sample of **12a** was obtained in 75% yield from **11a** by silica gel column chromatography using hexane/$CHCl_3$/AcOEt (1:1:1) as the eluent: mp 138−9 °C (AcOEt−hexane); IR (KBr) 3461, 1737 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 1.42 (t, 1H, J = 4.6 Hz), 2.18−2.39 (m, 1H), 2.91−3.21 (m, 3H), 3.40−3.65 (m, 2H), 3.80 (s, 3H), 3.86 (s, 3H), 5.16 (d, 1H, J = 9.2 Hz), 5.92 (s, 2H), 6.56−6.88 (m, 6H); MS m/z (relative intensity, %): 386 (M^+, 38), 194 (100), 135 (62). Anal. Calcd for $C_{21}H_{22}O_7$: C, 65.28; H, 5.74. Found: C, 65.08; H, 5.65

Stereoselective Deuteriation of the Metal Enolate of 3a. Deuteriation of **3a** (430 mg, 1.00 mmol in 5 mL) was carried out as described above for **1h** and **2h**. Compound **4d** and **4′d** was used directly for transformation into **1h** and **2h**.

(3R*,4S*,5R*)-3-Methyl-3-[3,4-(methylenedioxy)benzyl]-4-[[(methoxymethyl)oxy]methyl]-5-(3,4-dimethoxyphenyl)-γ-butyrolacetone (4e). Methylation of **3a** (500 mg, 1.16 mmol) was carried out as described above for **1i**. Crude product of **4e** was purified by silica gel column chromatography using hexane/$CHCl_3$/AcOEt (10:10:1) as the eluent to afford **4e** (450 mg, 87%): mp 101−2 °C (AcOEt−hexane); IR (KBr) 2945, 1757 cm^{-1}; 400 MHz ^1H NMR (δ in $CDCl_3$) 1.41 (s, 3H), 2.51−2.71 (m, 1H), 2.71 (d, 1H, J = 13.6 Hz), 3.29 (d, 1H, J = 13.6 Hz), 3.36 (s, 3H), 3.44 (dd, 1H, J = 4.6, 9.8 Hz), 3.61−3.76 (m, 1H), 3.67 (s, 3H), 3.84 (s, 3H), 4.55 (d, 1H, J = 6.6 Hz), 4.58 (d, 1H, J = 6.6 Hz), 4.83 (d, 1H, J = 10.2 Hz), 5.89 (d, 1H, J = 1.3 Hz), 5.90 (d, 1H, J = 1.3 Hz), 6.26 (d, 1H, J = 2.0 Hz), 6.62 (dd, 1H, J = 1.9, 8.1 Hz), 6.72 (s, 1H), 6.74 (s, 2H), 6.78 (s, 1H); MS m/z (relative intensity, %): 444 (M^+, 11), 135 (100), 45 (38). Anal. Calcd for $C_{24}H_{28}O_8$: C, 64.85; H, 6.35. Found: C, 64.72; H, 6.19.

Ethylation was conducted in the same manner described above.

(3R*,4S*,5R*)-3-Ethyl-3-[3,4-(methylenedioxy)benzyl]-4-[[(methoxymethyl)oxy]methyl]-5-(3,4-dimethoxyphenyl)-γ-butyrolactone (4f): 89% yield from **3a**; mp 112−3 °C (AcOEt−hexane); IR (KBr) 2945, 1757 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 1.16 (t, 3H, J = 7.5 Hz), 1.69−2.03 (m, 2H), 2.62 (d, 1H, J = 13.5 Hz), 2.63−2.79 (m, 1H), 3.35 (s, 3H), 3.38 (d, 1H, J = 13.6 Hz), 3.43 (dd, 1H, J = 4.6, 9.8 Hz), 3.65 (s, 3H), 3.74 (dd, 1H, J = 9.6, 10.9 Hz), 3.84 (s, 3H), 4.54 (d, 1H, J = 6.6 Hz), 4.58 (d, 1H, J = 6.6 Hz), 4.81 (d, 1H, J = 10.5 Hz), 5.84−5.94 (m, 2H), 6.21 (d, 1H, J = 1.9 Hz), 6.60 (dd, 1H, J = 2.0, 8.1 Hz), 6.72 (d, 1H, J = 8.2 Hz), 6.75 (br s, 2H), 6.81 (br s, 1H); MS m/z (relative intensity, %): 458 (M^+, 19), 135 (100). Anal. Calcd for $C_{25}H_{30}O_8$: C, 65.49; H, 6.60. Found: C, 65.28; H, 6.51.

(3S*,4S*,5R*)-3-Hydroxy-3-[3,4-(methylenedioxy)benzyl]-4-[[(methoxymethyl)oxy]methyl]-5-(3,4-dimethoxyphenyl)-γ-butyrolactone (4a). Hydroxylation of **3a** (7.00 g, 16.3 mmol) was carried out as described above for **1d**. Crude mixture of **4a**, which was purified by silica gel column chromatography using hexane/$CHCl_3$/AcOEt (5:5:3) as the eluent to afford **4a** (6.50 g, 89%) as a colorless crystalline solid: mp 122−4 °C (AcOEt−i-Pr_2O); IR (KBr) 3457, 1775 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 2.43−2.59 (m, 1H), 3.05 (d, 1H, J = 13.5 Hz), 3.16 (d, 1H, J = 13.4 Hz), 3.37 (s, 3H), 3.47 (s, 1H), 3.55 (dd, 1H, J = 4.2, 10.1 Hz), 3.76 (s, 3H), 3.79 (dd, 1H, J = 3.8, 10.1 Hz), 3.87 (s, 3H), 4.59 (d, 1H, J = 6.6 Hz), 4.63 (d, 1H, J = 6.5 Hz), 5.26 (d, 1H, J = 8.3 Hz), 5.92 (s, 2H), 6.46 (d, 1H, J = 13.4 Hz), 6.61−6.84 (m, 5H); MS m/z (relative intensity, %): 446 (M^+, 18), 238 (52), 193 (71), 165 (80), 135 (100). Anal. Calcd for $C_{23}H_{26}O_9$: C, 61.88; H, 5.87. Found: C, 61.71; H, 5.73.

(3R*,4S*)-3-Hydroxy-3-[3,4-(methylenedioxy)benzyl]-4-(3,4-dimethoxybenzyl)-γ-butyrolactone (2d). The lactone **4a** (0.72 g, 1.61 mmol) was dissolved in AcOH (10 mL), and 10% Pd/C (1.4 g) and concd H_2SO_4 (0.1 mL) were added to the solution. The mixture was stirred under hydrogen (3.5 atm, rt) for 48 h followed by filtration and evaporation to give a crude product (**13a**). To a solution of **13a** in a mixture of THF (3 mL), AcOH (3 mL), and water (3 mL) was added a catalytic amount of concd H_2SO_4, and the mixture was stirred for 3 h at 40 °C. The reaction mixture was cooled to rt, poured into water, extracted with AcOEt, dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed on silica gel with hexane/$CHCl_3$/AcOEt (5:5:3) as the eluent to afford **2d** as a solid in 85% yield. Recrystallization from AcOEt−hexane furnished pure **2d**. The diastereoselectivity was determined by HPLC analysis with 35:65 CH_3CN−H_2O as the mobile phase: mp 140−1 °C (AcOEt); IR (KBr) 3520, 1782 cm^{-1}; ^{1}H NMR (δ in CDCl$_3$) 2.64 (dd, 1H, J = 11.3, 13.3 Hz), 2.71 (s, 1H), 2.82−3.05 (m, 3H), 3.13 (dd, 1H, J = 3.9, 13.3 Hz), 3.87 (s, 3H), 3.88 (s, 3H), 3.93 (dd, 1H, J = 10.2, 10.2 Hz), 4.20 (dd, 1H, J = 7.7, 9.2 Hz), 5.96 (s, 2H), 6.63−6.87 (m, 6H); MS m/z (relative intensity, %): 368 (M$^+$, 10), 151 (9), 135 (100). Anal. Calcd for $C_{21}H_{22}O_7$: C, 65.28; H, 5.74. Found: C, 65.24; H, 5.61.

(3S*,4R*)-3-Deuterio-3-[3,4-(methylenedioxy)benzyl]-4-(3,4-dimethoxybenzyl)-γ-butyrolactone (2h): 76% yield from **4d**; mp 102−3 °C (AcOEt−hexane); IR (KBr) 1773 cm^{-1}; ^{1}H NMR (δ in CDCl$_3$) 2.32 (dd, 1H, J = 12.3, 13.3 Hz), 2.60−3.13 (m, 3H), 3.22 (d, 1H, J = 14.9 Hz), 3.84 (s, 3H), 3.85 (s, 3H), 3.96−4.12 (m, 2H), 5.96 (s, 2H), 6.53 (d, 1H, J = 1.9 Hz), 6.61 (dd, 1H, J = 1.9, 8.1 Hz), 6.71−6.87 (m, 4H); MS m/z (relative intensity, %): 371 (M$^+$, 51), 151 (67), 135 (100).

(3S*,4R*)-3-Methyl-3-[3,4-(methylenedioxy)benzyl]-4-(3,4-dimethoxybenzyl)-γ-butyrolactone (2i). 84% yield from **4e**; mp 141−2 °C (AcOEt−hexane); IR (KBr) 2909, 1773 cm^{-1}; ^{1}H NMR (δ in CDCl$_3$) 1.21 (s, 3H), 2.47−2.78 (m, 2H), 2.73 (d, 1H, J = 14.0 Hz), 2.88 (d, 1H, J = 14.1 Hz), 2.96 (dd, 1H, J = 4.5, 13.2 Hz), 3.78 (dd, 1H, J = 9.0, 9.7 Hz), 3.87 (s, 3H), 3.88 (s, 3H), 4.08 (dd, 1H, J = 7.3, 9.1 Hz), 5.95 (s, 2H), 6.61−6.87 (m, 6H); MS m/z (relative intensity, %): 384 (M$^+$, 15), 151 (23), 135 (100). Anal. Calcd for $C_{22}H_{24}O_6$: C, 68.74; H, 6.29. Found: C, 68.29; H, 6.35.

(3S*,4R*)-3-Ethyl-3-[3,4-(methylenedioxy)benzyl]-4-(3,4-dimethoxybenzyl)-γ-butyrolactone (2j): 83% yield from **4f**; mp 134−5 °C (AcOEt−hexane); IR (KBr) 2938, 1771 cm^{-1}; ^{1}H NMR (δ in CDCl$_3$) 0.92 (t, 3H, J = 7.4 Hz), 1.38−1.60 (m, 1H), 1.70−1.92 (m, 1H), 2.62−3.00 (m, 5H), 3.67−3.80 (m, 1H), 3.87 (s, 3H), 3.88 (s, 3H), 4.03−4.15 (m, 1H), 5.95 (s, 2H), 6.52−6.88 (m, 6H); MS m/z (relative intensity, %): 398 (M$^+$, 48), 151 (60), 135 (100). Anal. Calcd for $C_{23}H_{26}O_6$: C, 69.33; H, 6.58; Found: C, 69.36; H, 6.53.

(3R*,4S*)-3-Hydroxy-3-(3,4-dimethoxybenzyl)-4-[3,4-(methylenedioxy)benzyl]-γ-butyrolactone [2c: (±)-guayadequiol]: 76% yield from **4b**; mp 151−2 °C (AcOEt); IR (KBr) 3415, 1762 cm^{-1}; ^{1}H NMR (δ in CDCl$_3$) 2.64 (dd, 1H, J = 11.3, 13.1 Hz), 2.71 (s, 1H), 2.80−3.00 (m, 1H), 2.97 (s, 2H), 3.12 (dd, 1H, J = 3.9, 13.1 Hz), 3.86 (dd, 1H, J = 9.2, 10.2 Hz), 3.88 (s, 6H), 4.19 (dd, 1H, J = 7.7, 9.1 Hz), 5.95 (s, 2H), 6.60−6.90 (m, 6H); ^{13}C NMR (δ in CDCl$_3$) 32.18, 38.33, 48.21, 55.93, 55.98, 69.29, 75.87, 101.09, 108.56, 108.75, 111.36, 113.76, 121.36, 122.70, 125.60, 131.60, 146.56, 148.13, 148.75, 149.05, 177.80; MS m/z (relative intensity, %): 386 (M$^+$, 19), 151 (100), 135 (23). Anal. Calcd for $C_{21}H_{22}O_7$: C, 65.28; H, 5.74. Found: C, 65.11; H, 5.81.

X-ray Analyses.[25] X-ray analyses were performed by a AFC5R (Rigaku) with CuKα radiation. The structures were solved by a direct method (SHELXS-86 or MULTAN-80), and the atomic parameters were refined using a full matrix least-square method with anisotropic temperature factors for non H atoms. Crystal data of **1i**: a = 6.79(11), b = 9.91(16), c = 28.32(13) Å, α = 90.0(0), β = 93.1(11), γ = 90.0(0)°, U = 1904.3-(41) Å^3, monoclinic, $P2_1/c$ (Z = 4), D_x = 1.34 g/cm^3, final R = 0.054 (Rw = 0.038). Crystal data of **12a**: a = 17.81(1), b = 7.56(1), c = 14.32(2) Å, α = 90.0(0), β = 91.2(1), γ = 90.0(0)°, U = 1928.1(3) Å^3, monoclinic, $P2_1/a$ (Z = 4), D_x = 1.33 g/cm^3, final R = 0.056 (Rw = 0.057). Crystal data of **2i**: a = 16.77(2), b = 9.53(1), c = 12.82(2) Å, α = 90.0(0), β = 108.44(1), γ = 90.0(0)°, U = 1942.0(4) Å^3, monoclinic, $P2_1/c$ (Z = 4), D_x = 1.32 g/cm^3, final R = 0.072 (Rw = 0.069).

Acknowledgment. We thank Dr. A. Kinumaki, Dr. T. Da-te, and Mr. K. Okamura of our company who carried out the NMR analyses and the X-ray crystallographic analyses.

Supporting Information Available: Compound characterization data for **5b**, **1m**−**o**, **1e**−**g**, **2e**−**g**, **10b**,**c**, **11b**,**c**, **3b**,**c**, **4b**,**c**, **2a** and the ORTEP diagram for **12a** (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9601932

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[25] The author has deposited atomic coordinates for **1d**, **2d**, and **13d** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.