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A SYNTHESIS OF α-SUBSTITUTED *trans*-α, β-DIBENZYL-γ-BUTYROLACTONES: DIASTEREOFACIAL DIFFERENTIATION IN THE ELECTROPHILIC ATTACK ON THE METAL ENOLATES OF α, β-DIBENZYL-γ-BUTYROLACTONES

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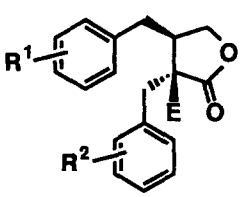
Summary: α-Substituted *trans*-α, β-dibenzyl-γ-butyrolactones were synthesized in a diastereoselective manner by the reaction of the potassium enolates of α, β–dibenzyl-γ-butyrolactones with electrophiles. The method was applied to the synthesis of (±)-trachelogenin.

Lignans of the *trans*-α, β-dibenzyl-γ-butyrolactone series bearing a hydroxyl group at the α-position, e. g., trachelogenin [**1d**(E=OH)][1], wikstromol [**1e**(E=OH)][2], have recently attracted considerable interest with the discovery of the exciting biological activities. The presence of the hydroxyl group *cis* to the β-benzyl group is crucial for exhibiting the biological activities[1]; for example, Ca^{2+} blocking action is observed for trachelogenin, but not for its stereoisomer, epitrachelogenin. In connection with our studies on search for a new lead compound having interesting biological activities, we now report a synthesis of a variety of α-substituted *trans*-α, β-dibenzyl-γ-butyrolactones(**1**) by electrophilic attack on the metal enolates of α, β-dibenzyl-γ-butyrolactones[3].



1: E=D, Me, Et, OH

a: R^1=3,4,5-$(OMe)_3$; R^2=3,4-OCH_2O

b: R^1=3,4-$(OMe)_2$; R^2=3,4-OCH_2O

c: R^1=3,4-$(OMe)_2$; R^2=3-OMe,4-OCH_2Ph

d: R^1=3,4-$(OMe)_2$; R^2=3-OMe,4-OH

e: R^1=R^2=3-OMe, 4-OH

Several reports have appeared on the stereoselective alkylation of the metal enolates of γ– or δ–lactones. It is well recognized that the electrophilic attack on the enolates of β-substituted γ-butyrolactones is controlled exclusively by the β-substituent leading to the *trans* addition products[4]. On the other hand, Koga and Tomioka reported the reverse diastereofacial differentiation in the alkylation of the enolates of α, β-disubstituted δ-valerolactones[5]; the facial preference is markedly affected by the exo-allylic substituent due to the 1,3-allylic strain[6] only when the

exo-allylic substituent is much bulkier than the β-substituent. We reasoned on the basis of the calculations of the minimum-energy conformations[7] of the enolate of **2** that the shielding of the bottom face by the phenyl group of the α-benzyl group due to the conformational rigidity induced by 1,3-allylic strain would be effective to allow the preferential attack of an electrophile from the upper face in spite of the presence of the β-benzyl group (**Fig. 1**)[8].

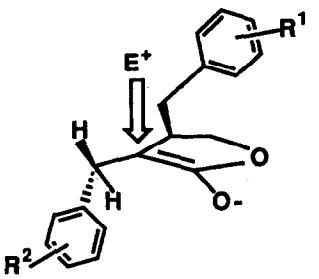
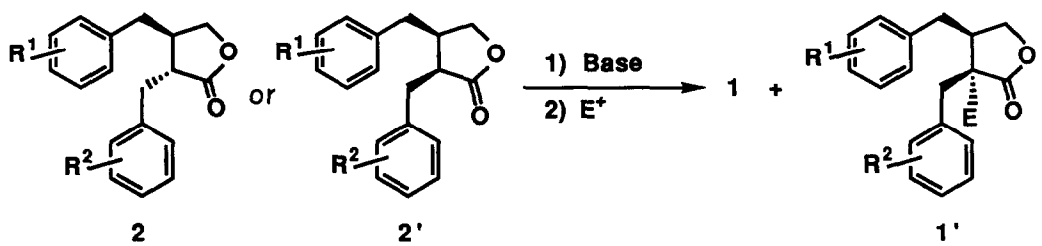


Fig. 1

Our study was begun with experiments to evaluate the degree of the diastereoselectivities in the electrophilic attack on the metal enolate of **2** and **2'** by using D_2O as a simple electrophile[9] (**Scheme 1**). The potassium enolate generated by the reaction of *trans*-α, β-dibenzyl-γ-butyrolactone (**2a**)[10] with potassium bis-(trimethylsilyl)amide (KHMDS) in THF at −78°C was treated with an excess amount of D_2O to afford **1a** (E=D) and **1'a** (E=D) in a ratio of 91: 9 (90% yield) (run 1 in Table 1): the ratio being determined based on the 400 MHz ^{1}H-NMR spectrum. This result indicates that the phenyl group of the α-benzyl group in the metal enolate of **2** is sterically bulky enough to allow the β-face entry of an electrophile. Furthermore, the potassium enolate generated from **2'a**[10] gave, as expected, almost the same diastereoselectivity as described above (run 2).



2 **2'** **1'**

Scheme 1

The results encouraged us to synthesize a variety of α-substituted *trans*-α, β-dibenzyl-γ-butyrolactones by this operation. Methylation and ethylation of **2b** proceeded in a stereoselective manner to give **1b** (E=Me) and **1b** (E=Et) as a major product, respectively. The yields and the ratios of the diastereoisomers are shown in Table 1 (runs 3, 4). The structures of these products were determined unambiguously by the 400 MHz ^{1}H-NMR spectra and/or the X-ray crystallography[11]. We next examined the hydroxylation[12] of **2** to synthesize trachelogenin and its related compounds. The

hydroxylation of **2** by using MoOPH[13] as an oxidizing agent, took place at −78°C to afford **1a** (E=OH) as a major product (run 5). It is noteworthy that the diastereoselectivity in the hydroxylation was improved to a considerable extent by addition of 18-crown-6 to the reaction mixture (run 6). Almost the same diastereoselectivity as above was observed in the hydroxylation of **2c** (run 7). Hydrogenolysis of compound **1c** (E=OH) over palladium charcoal in MeOH-THF at r.t. gave (±)-trachelogenin [**1d**(E=OH)] in a quantitative yield[14].

Table 1 Reactions of the enolates of **2** and **2'** with electrophiles[a]

run	Substrate	Electrophile	Product	Yield[b] (1+1')	Selectivity[c] (1 / 1')
1	**2a**	D_2O	**1a**(E=D)	90%	91/9
2	**2'a**	D_2O	**1a**(E=D)	91%	91/9
3	**2b**	MeI	**1b**(E=Me)	90%	94/6
4	**2b**	EtI	**1b**(E=Et)	77%	93/7
5	**2a**	MoOPH	**1a**(E=OH)	82%	63/37
6	**2a**[d]	MoOPH	**1a**(E=OH)	95%	83/17
7	**2c**[d]	MoOPH	**1c**(E=OH)	93%	82/18

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 NMR spectrum or HPLC of the crude reaction mixture. d) An equimolar amount of 18-crown-6 was added to the reaction mixture.

This method will be applied to the synthesis of various α-substituted *trans*-α, β-dibenzyl-γ-butyrolactones having intriguing biological activities. This report will also provide a significant example of the diastereofacial differentiation based on the concept of 1,3-allylic strain.

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References and Notes

1. Ichikawa, K.; Kinoshita, T.; Nishibe, S.; Sankawa, U. *Chem. Pham. Bull.* **1986**, *34*, (8), 3514.
2. Nishibe, S.; Hisada, S.; Inagaki, I. *Phytochemistry* **1971**, *10*, 2231.
3. Belletire and Fry reported the hydroxylation of α, β-bis(4-benzyloxy-3-methoxybenzyl)-γ-butyrolactone to synthesize wikstromol. In their report, they described that the stereoselectivity of this reaction was unexplainable and anomalous. From this result, they noted that the accepted structure of wikstromol might be in need of revision. See, Belletire, J. L.; Fry, D. J. *J. Org.*

Chem. **1988**, *53*, 4725. Shortly after this report had appeared, Brown *et al.* provided the definitive proof that the accepted structure need not be revised. See, Khamlach, L.; Dhal, R.; Brown, E. *Tetrahedron Lett.* **1989**, *30*, 2221.

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5. Tomioka, K.; Yasuda, K.; Kawasaki, H.; Koga, K. *Tetrahedron Lett.* **1986**, *27*, 3247 and references cited therein.
6. Tomioka, K.; Kawasaki, H.; Yasuda, K.; Koga, K. *J. Am. Chem. Soc.* **1988**, *110*, 3597.
7. The calculations were carried out by using MAXIMIN 2 in SYBYL and MNDO program from MOPAC to minimize the energetically possible conformations. To simplify the calculations, $-O^-Li^+$ was treated as $-O^-$ and the substituted phenyl group as non-substituted phenyl group. The dihedral angle (C^5-C^4-C^3-C^6) of the minimum-energy conformation was calculated to be 68°, when placing the C^1-H^a bond on the plane of the enolate (**Fig. 2**); the heat of formation of this conformation is -63.30 Kcal/mol.

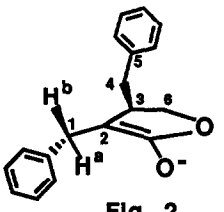

Fig. 2

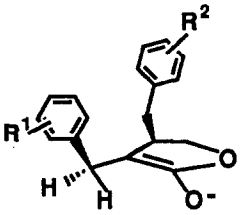

Fig. 3

8. The conformation shown in **Fig. 1** is more stable by a factor of 2 Kcal/mol than that shown in **Fig. 3**.
9. 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.
10. Compounds **2a-c** were synthesized by the conventional method. See, Lalami, K.; Dahl, R.; Brown, E. *Heterocycles* **1988**, *27*, 1131. Compound **2a'** was synthesized from 3-(3,4,5-trimethoxybenzyl)-γ-butyrolactone: i) LDA, piperonal; ii) Ac_2O, Et_3N; iii) NaH; iv) Pd-C/H_2.
11. The structure of **1b** (E=Me) was determined by the X-ray crystallography. For **1b** (E=Me), a 3% of NOE was observed between methyl proton and methylene proton of β-benzyl group in NOEDIF, but NOE was not observed for **1'b** (E=Me). Similar results were obtained for **1b** (E=Et).
12. Brown et al. reported the hydroxylation of the enolate of **2** with molecular oxygen. However, the diastereoselectivity was not observed in this reaction. See, ref. 3.
13. Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188.
14. The NMR spectrum of the product obtained here was completely consistent with that of trachelogenin shown in ref. 1.

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