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A Highly Stereoselective Synthesis of α-Substituted *cis*-α, β-Dibenzyl-γ-butyrolactones

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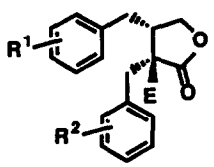
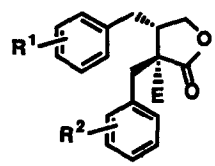
Abstract: α-Substituted *cis*-α, β-dibenzyl-γ-butyrolactones (1) were synthesized in good yields in a highly diastereoselective manner *via* electrophilic additions to the metal enolates of β, γ-disubstituted α-benzyl-γ-butyrolactones (2) as a key step.

Lignans of the α-substituted α, β-dibenzyl-γ-butyrolactone series, e.g., guayadequiol [1b (E=OH)], epitrachelogenin [1c (E=OH)], and trachelogenin [1'c (E=OH)], have recently attracted considerable interest because of their intriguing biological activities.[1,2] α-Hydroxy-*cis*-α, β-dibenzyl-γ-butyrolactones [1 (E=OH)] have been synthesized in a non-stereoselective manner by electrophilic additions to the metal enolates of α, β-dibenzyl-γ-butyrolactones.[3,4] We recently reported that electrophilic additions to the metal enolates of α, β-dibenzyl-γ-butyrolactones inevitably result in the preferential formation of α-substituted *trans*-α, β-dibenzyl-γ-butyrolactones (1') under any reaction condition due to the shielding effect of the α-benzyl group induced by the 1,3-allylic strain.[5-7] For this reason, a new approach is required to synthesize α-substituted *cis*-α, β-dibenzyl-γ-butyrolactones (1) stereoselectively. In connection with our efforts in search of new compounds having interesting biological activities,[8-10] we now report the first diastereoselective synthesis of α-substituted *cis*-α, β-dibenzyl-γ-butyrolactones (1) *via* electrophilic additions to the metal enolates of β, γ-disubstituted α-benzyl-γ-butyrolactones (2).



1a-d



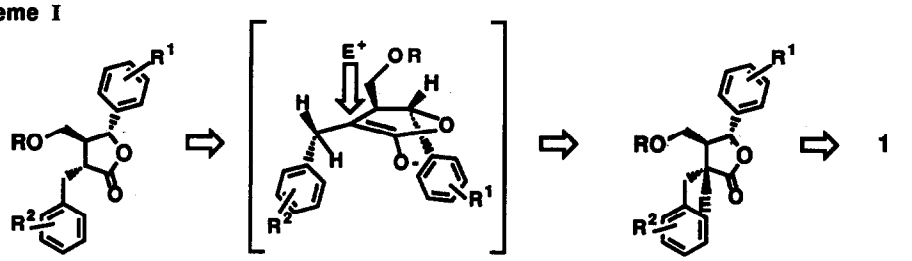
1'a-d

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

E=Me, OH

In **Scheme I** are illustrated the main features of our synthetic strategy involving the electrophilic addition to the metal enolate of **2** followed by construction of the desired product (**1**). We envisaged that the electrophilic attack on the metal enolate of **2** would occur predominantly from the upper face in spite of the presence of the methoxymethoxymethyl group due to the shielding effect of the α-benzyl group based on the 1,3-allylic strain; the stereoselectivity would be further increased by the γ-phenyl group. In order to evaluate our working hypothesis, the M.O. calculations were carried out for the transition structures in the electrophilic addition of methyl iodide to the metal enolate of β-methoxymethyl-α-benzyl-γ-butyrolactone which was used as a model compound. The results showed that the transition structure in the upper-face attack is more stable by approximately 3kcal/mol than that in the lower-face attack.[11]

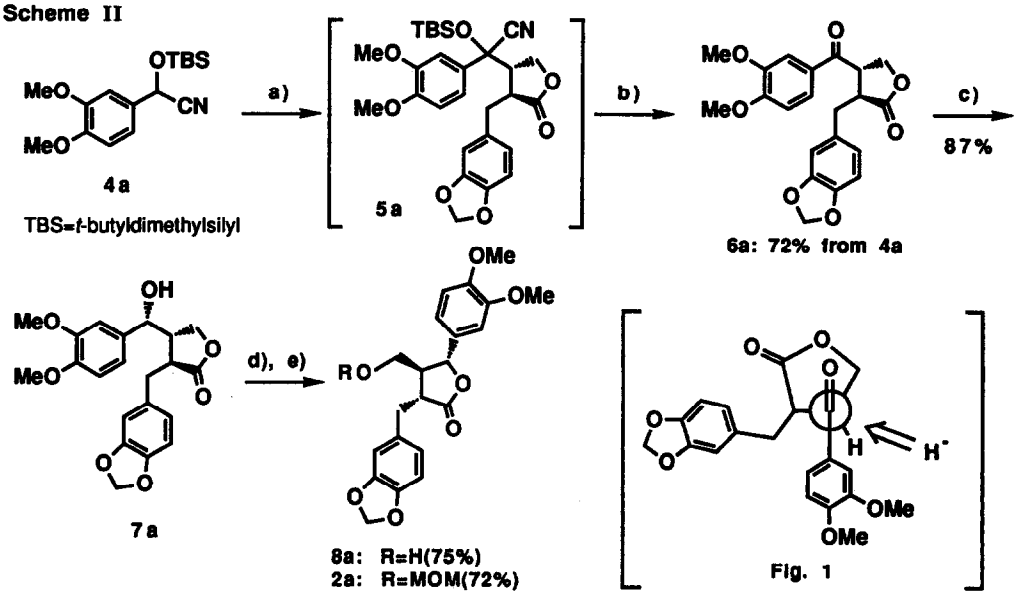
Scheme I



2 R=methoxymethyl(MOM) 3

The above result encouraged us to synthesize **1** based on our synthetic strategy. The requisite β, γ-disubstituted α-benzyl-γ-lactone (**2a**) was synthesized starting from *O*-silylated cyanohydrin (**4a**) (**Scheme II**). The conjugate addition of the lithium enolate of **4a** to butenolide at -78°C,[12] followed by trapping the resulting enolate with 3,4-methylenedioxybenzyl bromide gave **5a**. Without isolation of **5a**, the resulting mixture was treated with tetrabutylammonium fluoride to afford the *trans*-γ-butyrolactone (**6a**) (mp 151-152°C) in 72% yield. Reduction of **6a** with L-Selectride® occurred stereoselectively to give only the alcohol (**7a**) in 87% yield; the hydride would attack predominantly from the sterically less hindered side (**Fig. 1**). Treatment of **7a** with NaH in DMF afforded **8a** (mp 138-139°C) in 75% yield. The structure of **8a** was unambiguously determined by the X-ray crystallographic analysis; epimerization at the α-carbon of **8a** was found to take place completely during the rearrangement. The primary hydroxyl group of **8a** was protected by MOM group to afford the desired disubstituted α-benzyl-γ-lactone **2a** (mp 99-100°C) in 72% yield. **2b, d** were also synthesized by the same procedure as described above.

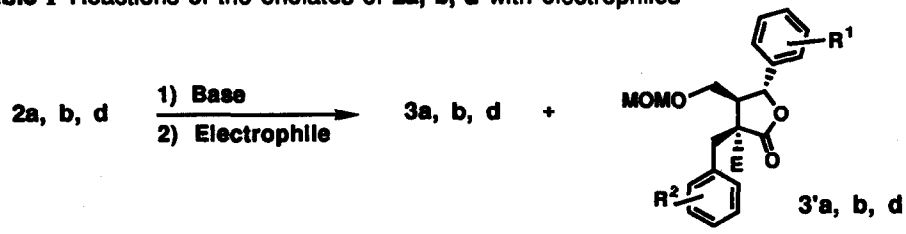
Scheme II



a) LDA, butenolide, 3, 4-methylenedioxybenzyl bromide / THF, -78~0°C; b) Bu_4NF-AcOH / CH_2Cl_2, 0°C; c) L-Selectride / THF, -78~-20°C; d) NaH / DMF, 0°C; e) MOMCl, *i*-Pr_2NEt / DMF, r.t.

We next examined electrophilic additions to the metal enolates of γ-butyrolactones (**2**). The potassium enolate generated by reaction of **2a** with potassium hexamethyldisilazane (KHMDS) in THF at -78°C was treated with methyl iodide to furnish **3a** (E=Me) in 90% yield, the ratio of **3a** (E=Me, mp 95-96°C)[13] to **3'a** (E=Me) being over 99 : 1 (entry 1 in Table I). Hydroxylation also proceeded in a highly stereoselective manner (entry 2, 3, 4). The results are summarized in **Table I**.

Table I Reactions of the enolates of **2a, b, d** with electrophiles[a)]

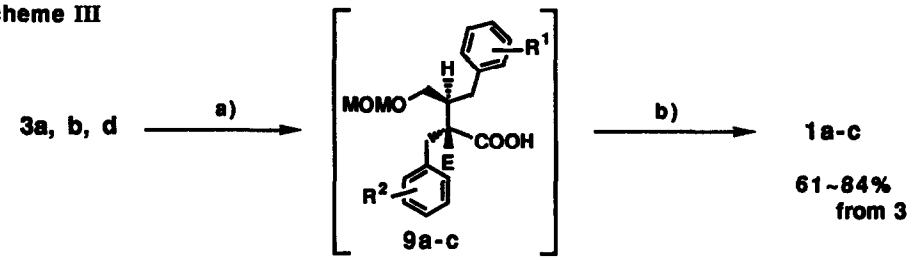


entry	substrate	electrophile	E	yield [b)] (3+3')	selectivity [c)] (3 / 3')
1	**2a**	MeI	E=Me	90%	>99/1
2	**2a**	MoOPH	E=OH	76%	99/1
3	**2b**	MoOPH	E=OH	70%	98/2
4	**2d**	MoOPH	E=OH	80%	98/2

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 HPLC (CAPCELL PAK C_{18}).

We finally investigated the conversion of the *trans*-product [**3a** (E=Me)] into the desired *cis*-product [**1a** (E=Me)] (**Scheme III**). Hydrogenolysis of **3a** (E=Me) using 10%-Pd on charcoal, followed by removal of the MOM group under the acidic conditions gave **1a** (E=Me, mp 144-145°C).[14] (±)-Guayadequiol [**1b** (E=OH, mp 151-152°C)][15] and epitrachelogenin [**1c** (E=OH, mp 128-129°C)] were also obtained from **3b** and **3d**, respectively, in good yields.

Scheme III



a) H_2, Pd-C / AcOH, r.t.; b) cat. H_2SO_4 / THF-AcOH-H_2O, 40°C

We presented the first highly diastereoselective synthesis of α-substituted *cis*-α, β-dibenzyl-γ-butyrolactones (**1**). This method should find application in the stereoselective synthesis of a variety of α-substituted *cis*-α, β-dibenzyl-γ-butyrolactones having intriguing biological activities.

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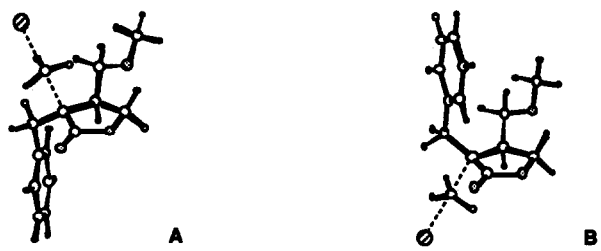
11. The calculations were carried out by using MAXIMIN 2 in SYBYL and MNDO program from MOPAC to minimize the energetically possible transition structures. In order to simplify the calculations, $-O^-K^+$ was treated as $-O^-$. The most stable transition structure A leading to the *trans*-isomer is more stable by 3.28 kcal/mol than the most stable transition structure B leading to the *cis*-isomer.



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13. A 9.5% of NOE was observed between the methyl protons and the γ-methine proton of **3a** (E=Me) in NOEDIF, while **3'a** (E=Me) showed no NOE.
14. The structure of **1a** (E=Me) was unambiguously determined by the X-ray crystallographic analysis. A 10.2% of NOE was observed between the methyl protons and the β-methine proton of **1a** (E=Me) in NOEDIF, while **1'a** (E=Me) showed no NOE.
15. The NMR spectrum of the product obtained here was completely consistent with that of (±)-guayadequiol reported in ref. 1.

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