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Diastereomer Differentiation during 1,2-Addition of Grignard Reagents Under Rotamer Distribution Control

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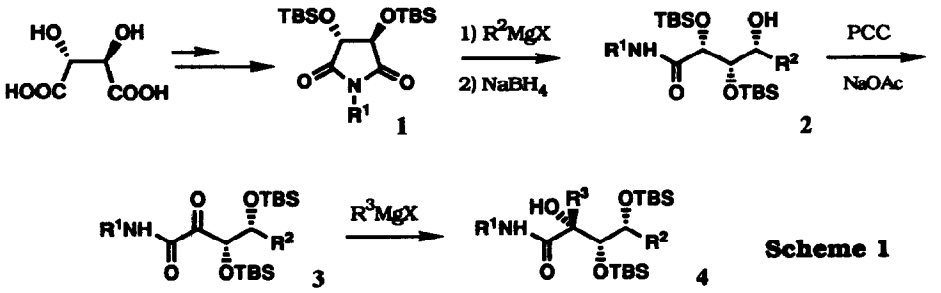
Abstract: *Construction of (R)-tertiary alcohols through diastereofacial differentiation under rotamer distribution control was accomplished with complete selectivity by means of simple nucleophilic addition of Grignard reagents to chiral α-ketoamides elaborated from C_2-symmetrical imides and the absolute configuration was established by an X-ray crystallographic analysis.*

The onset of molecular recognition during 1,2-asymmetric induction by nucleophilic addition of organometallic reagents to (pro-)chiral carbonyl compounds holds considerable interest[1] in the context of stereoselective alicyclic and heterocyclic synthesis.[2] And it is generally accepted that stereochemical relationships follow the interpretation proposed by using either Cram's chelation model or non chelation (Felkin-Anh or Conforth) model. Especially, the stereochemistry observed by the reaction with α-alkoxy carbonyl compounds strongly depends on the nature of organometallics and the protecting group of α-hydroxy function employed.[3] In addition, since an extremely efficient method for controlling ground-state rotamer distribution has been recently developed by Saito et al. using vicinal diol controller,[4] such diastereofacial differentiation has been of major interest with respect to the extensive elucidation of the mechanistic aspects.

As part of our program designed to explore the use of cyclic imides, we demonstrated a significant diastereomer differentiating reaction based on the successive alkylation and reduction of chiral C_2-symmetrical imides **1**[5] and its application to the total synthesis of natural antibiotic, (+)-cerulenin.[6] The central feature of the present communication is to describe that chiral ketones **3** bearing contiguous stereogenic centers underwent extremely high diastereospecific addition with various Grignard reagents under rotamer distribution control and the absolute configuration of the adducts **4** was unambiguously confirmed to be R by the use of X-ray analysis.

As shown in Scheme 1, treatment of chiral imides **1** according to our previous reports[5,6] afforded **2**, which were successively submitted to the PCC oxidation in the presence of sodium acetate, leading to the interesting α-ketoamides **3** with 1,5-silyl rearrangement.[7] Accompanying formation of the normally oxidized products was not observed in this reaction. Initially, nucleophilic addition of methylmagnesium bromide to **3** was carried out under various conditions and the results are summarized in Table 1. Finally, a highly diastereospecific reaction (95 : 5) was achieved at low temperature by using THF as the solvent within one hour (Entry 4) to furnish the product **4a** predominantly.



Scheme 1

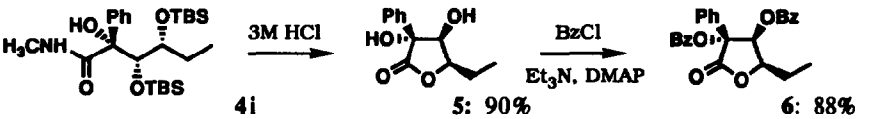
Table 1. Preparation of Chiral Ketones 3 and Reaction with Grignard Reagents

Entry	R^1	R^2 a)	R^3 a)	Yield of 3 / % b)	Solvent	Temp / °C (Time / h)	Yield of 4 / % c)	Diastereomer ratio d)
1	Me	Oct	Me	46	toluene	-78 (1)	72 (4a)	35 : 65
2	Me	Oct	Me	--	ether	-78 (1)	84 (4a)	46 : 54
3	Me	Oct	Me	--	THF	0 (1)	100 (4a)	87 : 13
4	Me	Oct	Me	--	THF	-78 (1)	90 (4a)	95 : 5
5	Bn	Oct	Me	50	THF	-100 (1)	37 (4b)	67 : 33
6	Me	Et	Me	70	THF	-100 (1)	97 (4c)	94 : 6 e)
7	Me	Oct	Et	--	THF	-100 (1)	34 (4d)	> 99 : 1
8	Me	Et	Oct		THF	-100 (1)	54 (4e)	> 99 : 1
9	Me	Oct	Methallyl	--	THF	-100 (0.5)	87 (4f)	99 : 1
10	Me	Methallyl	Oct	32	THF	-100 (0.5)	59 (4g)	> 99 : 1
11	Me	Allyl	Ph	35 f)	THF	-100 (1)	40 (4h)	> 99 : 1
12	Me	Et	Ph	--	THF	-100 (1)	27 (4i)	> 99 : 1
13	Me	Et	Methallyl	--	THF	-100 (0.5)	77 (4j)	> 99 : 1
14	Me	Methallyl	Et	--	THF	-100 (0.5)	55 (4k)	> 99 : 1

a) 2-4 equiv. of reagents were used. b) Isolated yield based on **1**. c) Isolated yield. d) Determined by HPLC (Cosmosil Sil). e) Determined after cyclization to the lactone. f) 2 : 3 mixture of allyl and propyl groups, the latter resulted from the hydrogenation under reduction conditions.

Furthermore, it has become apparent that in most cases (except R^3=Me) complete stereodifferentiation was observed by means of simple Grignard addition (Entries 7-14) and this procedure is applicable for the production of a wide range of chiral quarternary α-hydroxy carbonyl compounds. However, the attacking face of organometallic reagents to the carbonyl function remains ambiguous.

Since several attempts to determine the absolute configuration of these Grignard adducts by transformation into a known compound did not afford the desired results, this structural assignment was performed by X-ray crystallographic analysis. As shown in Scheme 2, hydroxyamide **4i** was cyclized under acidic conditions followed by deprotection to provide the diollactone **5**, which was subjected to bis-benzoylation, leading to the corresponding crystalline **6**. Thus, the structure and stereochemical relationship was established to be **R** configuration by an X-ray analysis of **6** (Fig. 1) and the other compounds were also identified by comparison with the observed chemical shift and similarities in their NMR spectra.



4i **5**: 90% **6**: 88%

Scheme 2

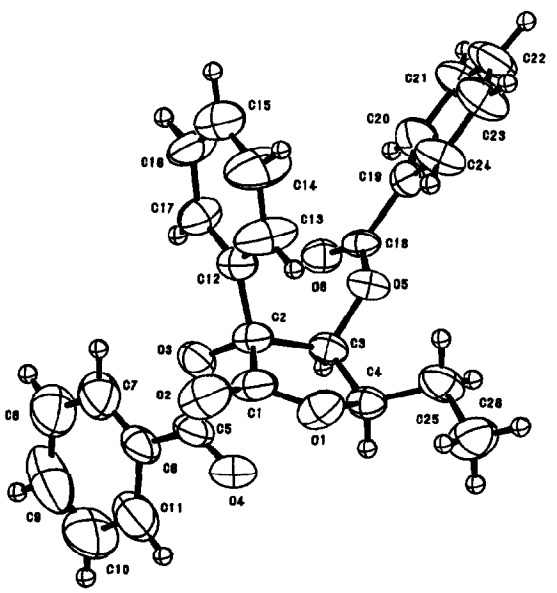


Fig. 1 ORTEP drawing of the lactone **6**

With the observed stereochemical outcome in hand, these results strongly support the concept that the reaction proceeds under the control of rotamer distribution containing a 5-membered chelation structure due to the steric repulsion in analogy with disclosed results,[4,5] in which the both large silyl groups occupy remote positions (Fig. 2). Then, nucleophilic addition would be established through the attack to the carbonyl group from the top face of the planar chelation structure.

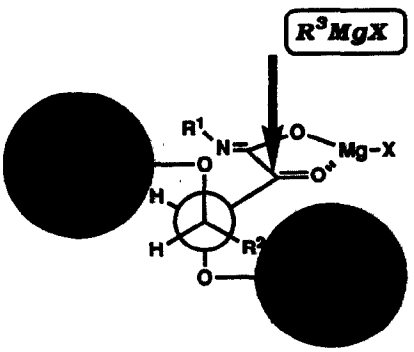


Fig.2 Structure model of intermediate

In summary, an efficient method for the stereoselective synthesis of the quarternary α-hydroxy carbonyl compounds with contiguous tertiary centers has been developed. This procedure will find application in the synthesis of polyhydroxylated biological products.

Acknowledgment: We deeply appreciate Professor S. Saito (Okayama University) for the valuable discussions.

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7. It is not necessary to remove the minor C-4 stereoisomer from **2** prior to oxidation since no other isomeric compound was observed when the mixture was allowed to react. The reason is not clarified at present, but it would be attributable to the special steric interaction between the large two silyl groups.