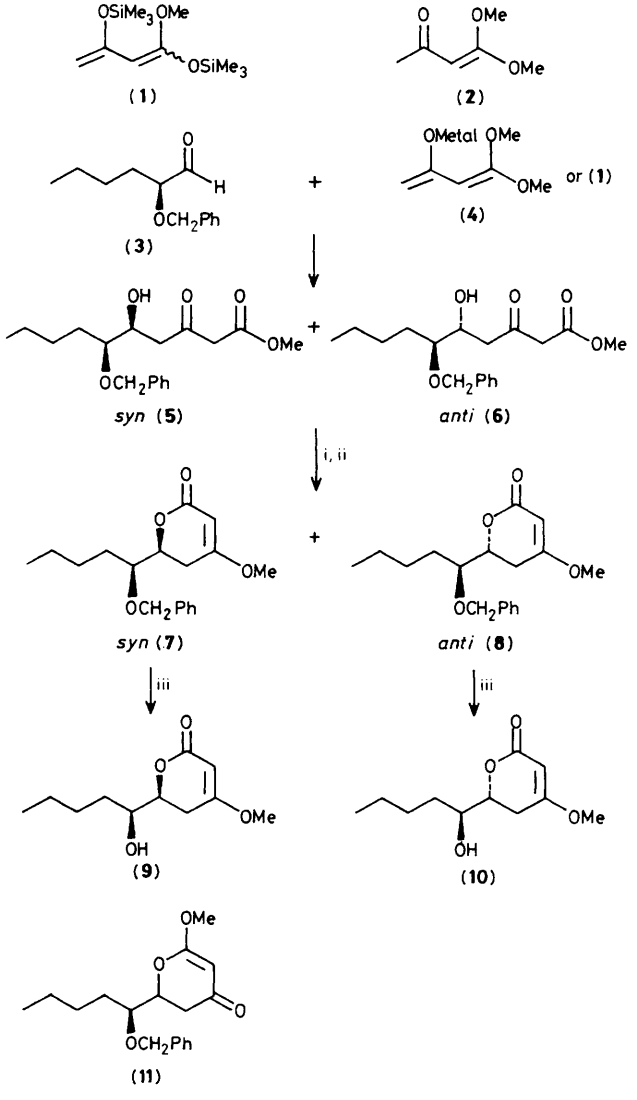
Highly Diastereoselective Titanium Tetrachloride-mediated Aldol Condensation of the Bistrimethylsilyl Enol Ether of Acetoacetic Ester with 2-Benzyloxyhexanal. A Synthesis of (−)-Pestalotin

Hisahiro Hagiwara,* Katsuhiko Kimura, and Hisashi Uda

Chemical Research Institute of Non-aqueous Solutions, Tohoku University, Katahira, Sendai 980, Japan

Titanium tetrachloride-mediated aldol condensation of the bistrimethylsilyl enol ether of methyl acetoacetate (**1**) with 2-benzyloxyhexanal (**3**) gives highly selectively (99 : 1) the *syn* aldol adduct (**5**); the stereocontrolled synthesis of (−)-pestalotin (**9**) has been accomplished.

During the past decade, a great deal of effort has been devoted to the control of the stereochemistry of cross aldol condensation reactions between two acyclic carbonyl components.[1] A current topic is the synthesis of the *syn* 1,2-glycol derivatives from 2-alkoxyaldehydes with ester enolates or enols under chelation control (Cram-cyclic mode).[2] There are also a few reports concerning the chelation controlled aldol condensation of ketone enolates or enol ethers.[3] Simple methyl ketone derivatives have rarely been used as nucleophiles probably owing to low stereoselectivity due to the lack of an extra group at the reacting termini. In connection with our interest in designing structural features of natural products by the aldol condensation of 2-alkoxycarbonyl compounds,[4] we disclose herein the highly diastereoselective Lewis acid-mediated aldol condensation of the bistrimethylsilyl enol ether of methyl acetoacetate (**1**) with 2-benzyloxyhexanal (**3**) under chelation control leading to the *syn* 1,2-glycol derivative (**5**), and its application to the synthesis of (6*S*,1′*S*)-(−)-pestalotin (**9**),[5] known as a gibberellin synergist.



Scheme 1. *Reagents:* i, aq. NaOH/tetrahydrofuran (THF), then H_3O^+; ii, Me_2SO_4, K_2CO_3/acetone [72% from (**5**) and (**6**)]; iii, H_2, 5% Pd/C/AcOEt (65%).

The aldol condensation of two acetoacetic ester equivalents, the acetal (**2**)[6] and the bistrimethylsilyl enol ether (**1**),[7] with (±)-2-benzyloxyhexanal (**3**) were investigated under various reaction conditions. The diastereoisomeric ratios of the adducts (**5**) and (**6**) were determined by preparative h.p.l.c. separation of the lactonic methyl ethers (**7**) and (**8**), which were derived from the inseparable mixture of (**5**) and (**6**) by lactonization and then methylation, and the relative configurations were unambiguously confirmed by transformation of (**7**) and (**8**) into (±)-pestalotin (**9**) and (±)-epi-pestalotin (**10**) (Scheme 1).

Initially, the reaction of the metal enolate (**4**) derived from the acetal (**2**) with 2-benzyloxyhexanal (**3**) was attempted, and the results are summarized in Table 1. As seen from Table 1, in contrast to the successful example of chelation controlled Grignard-type reactions,[8] the *anti* glycol derivative (**6**) was produced with modest selectivity.†

On the other hand, it was found that the Lewis acid-promoted aldol condensation of the bistrimethylsilyl enol ether (**1**) resulted in diastereochemical reversal. Thus, the *syn* glycol derivative (**5**) was produced preferentially as shown in Table 2. In particular, excellent diastereofacial selectivity (98%) was achieved when (**3**) (1 equiv.) was treated with $TiCl_4$ (1 equiv.) in CH_2Cl_2 between −86 and −82 °C for 5 min, followed by addition of the enol ether (**1**) (1.5 equiv.) at −80 °C (Table 2, entry 1). Since no selectivity was observed in the reaction by adding $TiCl_4$ to the mixture of (**1**) and (**3**) (Table 2, entry 6), it is the initial complexation of the benzyloxyaldehyde moiety of (**3**) with $TiCl_4$ that is responsible

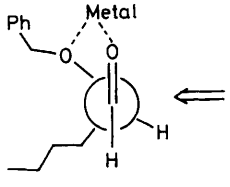


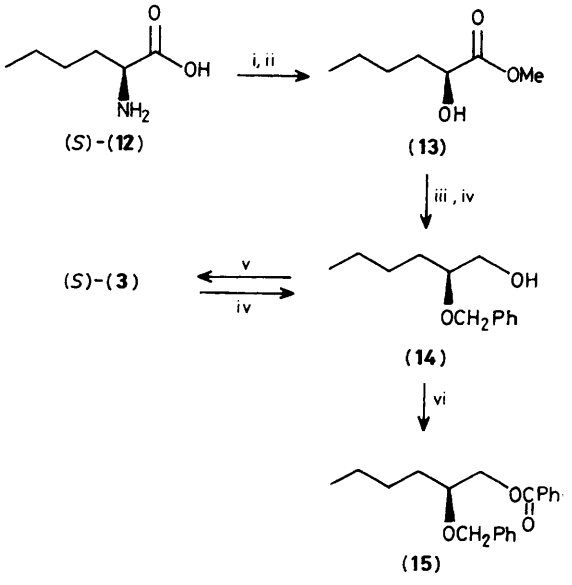
Figure 1

† The selectivity was not affected by changing the protecting group of 2-hydroxyhexanal into a MEM (methoxyethoxymethyl) or THP (tetrahydropyran-2-yl) ether.

Table 1. Aldol condensation of the metal enolate (**4**) with (**3**).

Entry	Metal	Solvent	Product ratio *syn* (**5**): *anti* (**6**)	Yield (%)
1	Li	THF	36 : 64	43
2		Et_2O[a]	49 : 51	25
3	Mg	Pentane/Et_2O[a] (3 : 1)	25 : 75	16
4		THF[b]	32 : 68	61

[a] $MgBr_2$ and then (**3**) were added to the lithium enolate of (**2**) between −90 and −80 °C. [b] The lithium enolate (**4**) was added to the mixture of $MgBr_2$ and (**3**).



Scheme 2. *Reagents:* i, $NaNO_2$, H_2SO_4 (71%); ii, CH_2N_2 (quant.); iii, Ag_2O, $PhCH_2Br/Et_2O$; iv, $LiAlH_4$ [74% from (**13**)]; v, $(COCl)_2$, Me_2SO, Et_3N/CH_2Cl_2 (44%); vi, PhCOCl, Pr^i_2NEt (82%).

for the high *syn* diastereoselectivity (Figure 1). In the case of $ZnCl_2$ (Table 2, entry 5), the reaction partially proceeded *via* the Danishefsky type hetero Diels–Alder process,[9] as judged from the isolation of a dihydropyrone derivative (**11**) along with the aldol products, the trimethylsilyl ethers of (**5**) and (**6**).

We then synthesized pestalotin (**9**) in natural enantiomeric form [(6*S*,1′*S*)-(−)], by using optically active (*S*)-(−)-2-benzyloxyhexanal (**3**). Compound (*S*)-(−)-(**3**), $[\alpha]_D$ −84.9° (*c* 1.433, $CHCl_3$), was prepared in five steps starting from (*S*)-(−)-2-aminohexanoic acid (L-norleucine) (**12**) as shown in Scheme 2. The optical purity [98% enantiomeric excess (e.e.)] was determined by h.p.l.c. analysis‡ of the benzyloxybenzoate (**15**), prepared from the alcohol (**14**) obtained by $LiAlH_4$ reduction of the (*S*)-aldehyde (**3**) immediately after its preparation by the Swern oxidation of (**14**). Thus, according to the procedure used for the racemic compound (Scheme 1), (6*S*,1′*S*)-(−)-pestalotin (**9**), $[\alpha]_D$ −80.3° (*c* 0.462, MeOH) {lit.[5c] $[\alpha]_D$ −91.7° (*c* 1.17, MeOH)},§ was obtained in 31% overall yield. Decrease in the optical purity (88% e.e.) of (**9**) showed that epimerization of (*S*)-(**3**) occurred slightly during this aldol condensation reaction.

‡ A chiral column [Chiralpak OT(+)®] with 95% aq. MeOH was used.

Table 2. Diastereoselective aldol condensation of (**1**) with (**3**).[a]

Entry	Lewis acid	Product ratio *syn* (**5**): *anti* (**6**)	Yield (%)
1	$TiCl_4$	99 : 1	66
2	$SnCl_4$	89 : 11	56
3	$BF_3{\cdot}OEt_2$	71 : 29	79
4	$EtAlCl_2$	53 : 47	42
5	$ZnCl_2$[b]	86 : 14	37
6	$TiCl_4$[c]	54 : 46	80

[a] All reactions except entry 6 were carried out, under N_2, in the same manner as the case of entry 1 described in the text. The reaction was quenched at −70 °C with water after stirring for 30 min. [b] Compound (**11**) and the silyl ethers of (**5**) and (**6**) were isolated. [c] $TiCl_4$ was added to the mixture of (**1**) and (**3**).

In conclusion, the present aldol condensation offers a convenient method for the preparation of synthetically useful δ,ε-*syn*-dihydroxy-β-ketoester derivatives in optically active form.

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§ The highest specific rotation of (−)-pestalotin (**9**) was obtained by repeated recrystallisation from diethyl ether–hexane {$[\alpha]_D$ −93.7° (*c* 0.127, MeOH)}.