

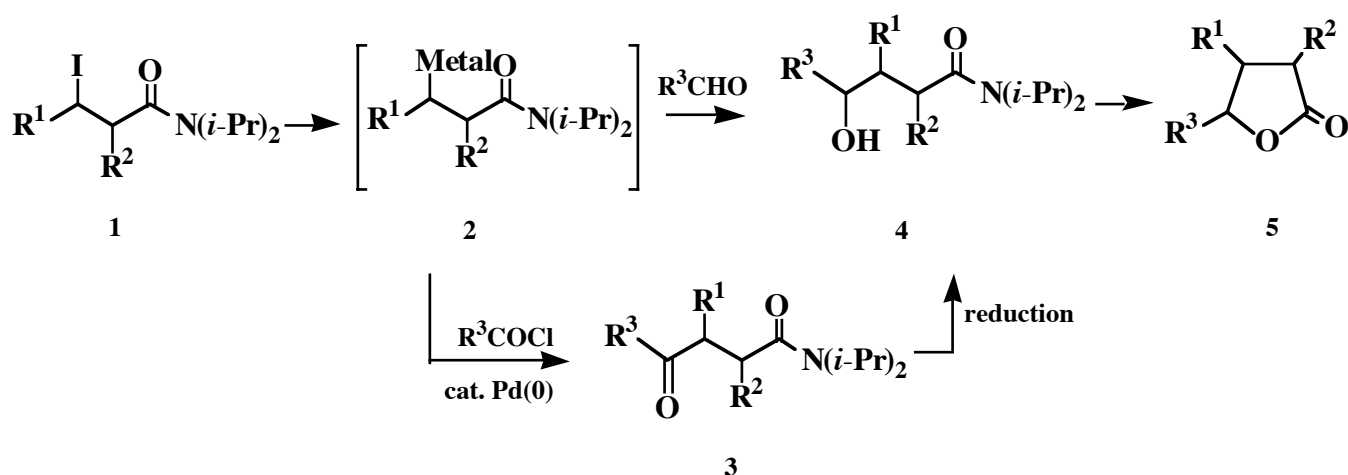
HIGHLY DIASTEREOSELECTIVE REDUCTION OF γ -KETO AMIDES: DIASTEREOSELECTIVE SYNTHESIS OF γ -BUTYROLACTONES WITH CONTIGUOUS CHIRAL CENTERS

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Abstract - Diastereoselective reduction of γ -keto amides, which were easily prepared by the reaction of a zinc homoenolate of butanamide with acid chlorides in the presence of Pd(0) catalyst, was achieved. Cyclization of the products, γ -hydroxy amides, under various conditions gave α,β -disubstituted and α,β,γ -trisubstituted γ -butyrolactones with high diastereoisomeric purities.

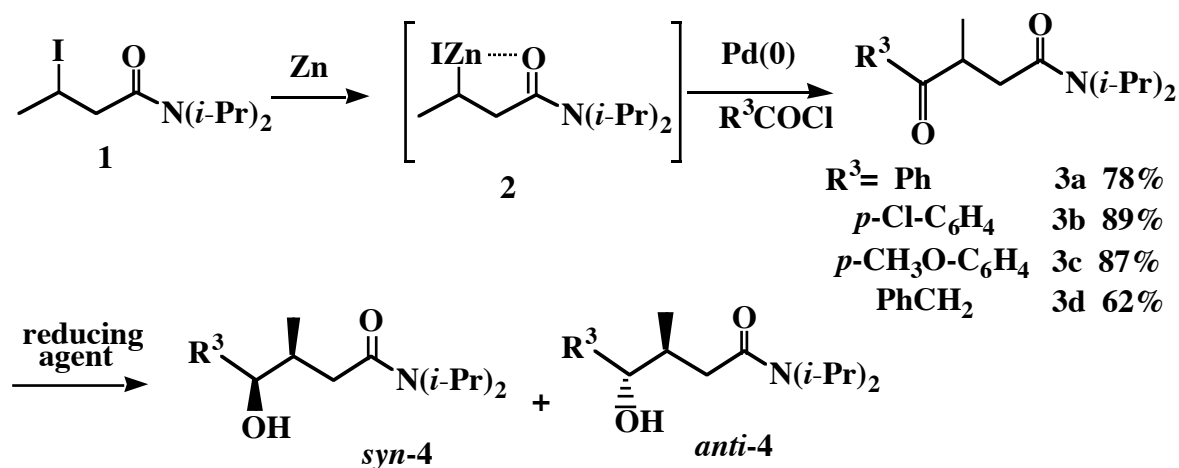
In a previous paper,¹ we reported that amide homoenolates (**2**) [Metal=ZnI or TiCl(OiPr)₂] reacted with aldehydes to give γ -hydroxy amides (**4**) with good to high diastereoisomeric purities (R¹=Me, R²=H, *syn: anti*=97:3~13:87). However, the stereoselectivity seems to be still problematic in synthetic viewpoints. Therefore, an alternative stereoselective approach to γ -hydroxy amides (**4**), which ultimately give lactones (**5**), *via* reduction of γ -keto amides (**3**) was targeted.



Scheme 1

In contrast to abundant reports on the diastereoselective reduction of α -alkylated β -keto amides or esters,²⁻¹⁰ only few reports on the reduction of β -alkylated γ -keto amides or esters have appeared.¹¹⁻¹⁵

γ -Keto amide (**3a-3d**) was easily obtained by the Pd(0) catalyzed acylation of zinc homoenolate (**2**) with acid chlorides in 62-89% yields.¹⁶ First, the reduction of **3a** (R³=Ph) was investigated. Among various reducing agents and conditions examined (Table 1 entries 1-8), use of diisobutylaluminum hydride (DIBAH) in THF at -78 °C was the best choice to give *syn*-**4** exclusively (entry 8). Under the same reaction conditions, other γ -keto amides also gave *syn*-**4** in high yields (entries 9-11).



Scheme 2

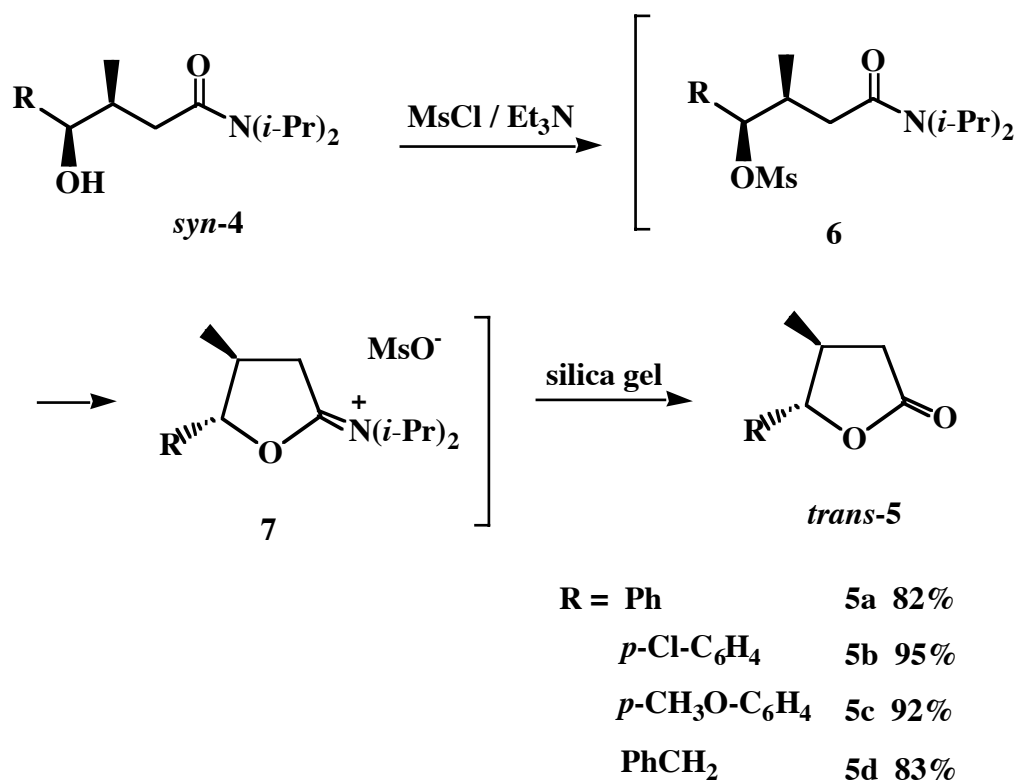
Table 1 Reduction of β -substituted γ -keto amides (**3a~d**) under various conditions.

entry	R ³	3	reducing agent	solvent	temp (°C)	time (min)	yield 4 (%)	ratio ^{a)} <i>syn</i> : <i>anti</i>
1	Ph	3a	LiAlH ₄	THF	-18	15	98 ^{b)}	78 : 22
2	Ph		LiAlH ₄	THF	-78~-32	240	79 ^{b)}	76 : 24
3	Ph		LiAlH ₄	Et ₂ O	-78	10	41 ^{b)}	88 : 12
4	Ph		NaBH ₄	MeOH	-8	10	99 ^{b)}	74 : 26
5	Ph		L-selectride	THF	-78	10	39 ^{b)}	74 : 26
6	Ph		Zn(BH ₄) ₂	Et ₂ O	0	10	76 ^{b)}	92 : 8
7	Ph		<i>i</i> -Bu ₂ AlH	toluene	-78	10	91 ^{b)}	93 : 7
8	Ph		<i>i</i> -Bu ₂ AlH	THF	-78	10	87	100 : 0
9	<i>p</i> -Cl-C ₆ H ₄	3b	<i>i</i> -Bu ₂ AlH	THF	-78	10	93	100 : 0
10	<i>p</i> -CH ₃ O-C ₆ H ₄	3c	<i>i</i> -Bu ₂ AlH	THF	-78	10	90	100 : 0
11	PhCH ₂	3d	<i>i</i> -Bu ₂ AlH	THF	-78	10	62	100 : 0

a) Determined by 400 MHz NMR and/or HPLC.

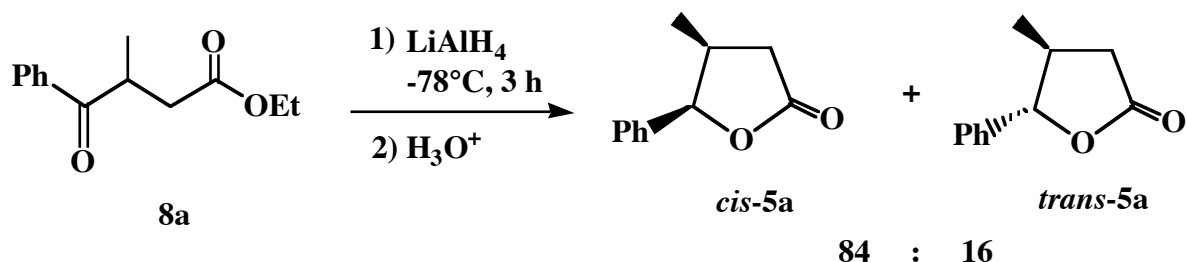
b) Yield of a mixture of diastereoisomers.

With diastereomerically pure γ -hydroxy amides (*syn-4*) in our hands, transformation into the corresponding γ -lactones was then examined. Unfortunately, acid catalyzed cyclization of *syn-4* leading to sterically unfavorable *cis*-lactones was found to be non-stereoselective. For example, treatment of *syn-4a* in refluxing THF for 7.5 h in the presence of *p*-toluenesulfonic acid (3.6 eq), a 2:1 mixture of *cis-5a* and *trans-5a* was obtained in a fair yield. Then, we envisioned to cyclize with inversion of configuration at hydroxy group attached carbon. *Syn-4a* was mesylated with triethylamine and methanesulfonyl chloride in dichloromethane at 0 °C for 0.5-1 h. Intramolecular S_N2 displacement of mesylate (**6**) leading to ammonium salt (**7**) occurred under the mesylation conditions. Acid hydrolysis of the ammonium salt with strong acid such as HCl, H₂SO₄, and *p*-toluenesulfonic acid resulted in a failure. After mesylation, the reaction mixture was absorbed on silica gel and stood at roomtemperature for 1-3 days to give diastereomerically pure *trans-5* in 82-95 % yields (Scheme 3).



Scheme 3

When ethyl β -benzoylbutanoate (**8a**) was used instead of amide derivative (**3a**), the diastereoselectivity of the carbonyl reduction was unsatisfactory (84:16~65:35), i.e. among the reduction conditions with DIBAH, Zn(BH₄)₂, LiAlH₂(OEt)₂, LiAlH₄, and NaBH₄ in various solvents (THF, Et₂O, toluene, MeOH, and EtOH) at the temperature range of -78~0 °C, the best selectivity was obtained when reduction was carried out with LiAlH₄ in toluene-Et₂O (1:1) at -78 °C for 3 h and quenched with 2M HCl to give an 84 :16 mixture of *cis* and *trans* lactones in 54% yield (Scheme 4).

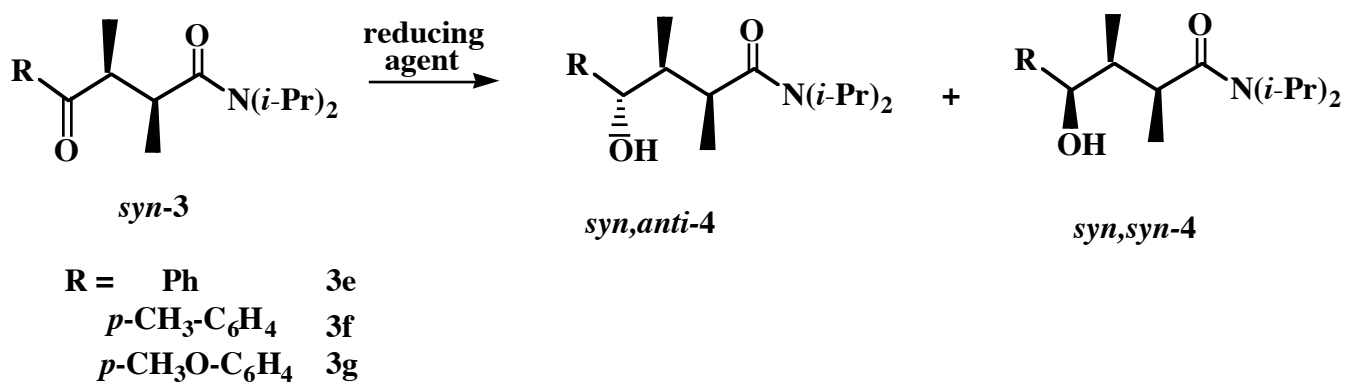


Scheme 4

For the stereoselective synthesis of lactones with three contiguous chiral carbon centers, the diastereoselective reduction of α,β -disubstituted γ -keto amide (**3**: $R^1, R^2 = \text{Me}$) was examined (Scheme 5). Reduction of *syn*-**3e** ($R = \text{Ph}$), which can easily be prepared,¹⁶ with DIBALH in THF or toluene at -78°C -room temperature resulted in a recovery of the starting material, presumably due to its structural congestion.

Use of LiAlH_4 (8 eq) in THF at -20°C for 0.5 h gave reduced products successfully, however, the diastereoselectivity was 84:16 (Table 2 entry 1). The reduction with 3.5 eq of L-selectride (lithium *trisec*-butylborohydride) in THF proceeded at -78°C , and after 2 h, almost exclusive formation of single diastereoisomer was observed (entry 2). The reduction of *syn*-**3f** ($R = p\text{-Tol}$) and *syn*-**3g** ($R = p\text{-CH}_3\text{O-C}_6\text{H}_4$) also proceeded in a similar manner to give the corresponding γ -hydroxy amides (entries 3 and 4). On the other hand, the reduction with $\text{Zn}(\text{BH}_4)_2$ (6 eq) in ether at 0°C for 4-9 h resulted in a preferential formation of another diastereoisomer (23:77-12:88, entries 5-7).

Since all of the above diastereoisomers are chromatographically easily separable, both diastereoisomers are obtained in a pure form.



Scheme 5

Table 2 Reduction of α,β -disubstituted γ -keto amides (**3e~g**).

entry	3	reducing agent	solvent	temp (°C)	time (h)	yield 4 (%)	<i>syn,anti</i> : <i>syn,syn</i>
1	3e	LiAlH ₄	THF	-20	0.5	100 ^{a)}	84 : 16 ^{b)}
2		L-selectride	THF	-78	2	97	97 : 3 ^{c)}
3	3f	L-selectride	THF	-78	2	95	99 : 1 ^{d)}
4	3g	L-selectride	THF	-78	3	73	95 : 5 ^{c)}
5	3e	Zn(BH ₄) ₂	Et ₂ O	0	4	98 ^{a)}	23 : 77 ^{b)}
6	3f	Zn(BH ₄) ₂	Et ₂ O	0	9	86 ^{a)}	12 : 88 ^{b)}
7	3g	Zn(BH ₄) ₂	Et ₂ O	0	9	71 ^{a)}	16 : 84 ^{b)}

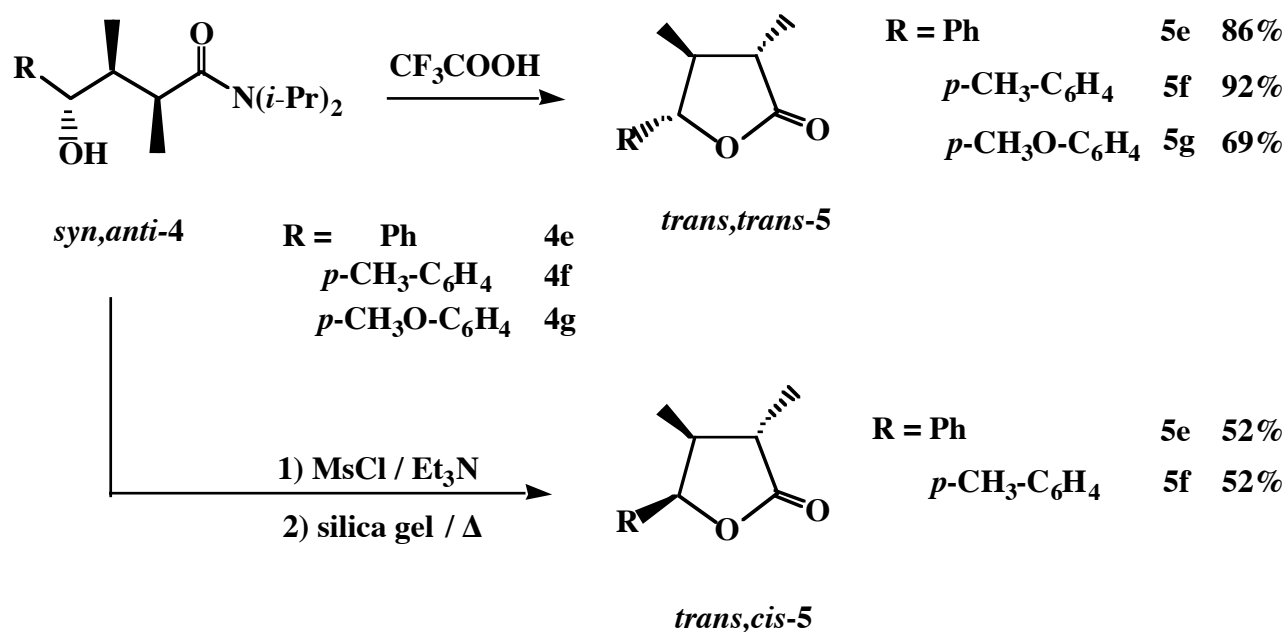
a) Combined yield of purified diastereoisomers.

b) Ratio of isolated isomers.

c) Determined by 400MHz NMR.

d) Determined by HPLC analysis.

Lactonization of *syn,anti-4e~g* under acidic conditions (at 65°C for 10-15 h in a 3:1 mixture of THF-CF₃COOH) gave the corresponding γ -butyrolactones with three contiguous chiral centers (*trans,trans-5e~g*) in high to good yields (Scheme 6). The lactonization of *syn,anti-4e~g* via the corresponding mesylates as mentioned before was also examined. In the present case, mesylation proceeded under similar reaction conditions, however, hydrolysis of the intermediary ammonium salt in the presence of silica gel was extremely sluggish. For example, in the case of *syn,anti-4e*, silica gel treatment at room temperature for 36 h gave *trans,cis-5e* in only 5% yield. Therefore, heating for 24 h at reflux was necessary to give *trans,cis-5e* in good yield (52%). Almost the same results were obtained for *syn,anti-4f* (R=*p*-Tol). However, in the case of *syn,anti-4g* (R=*p*-CH₃O-C₆H₄), heating for 24 h gave a 3:1 mixture of *trans,trans-5g* and *trans,cis-5g* in a poor (30%) yield (Scheme 6).



Scheme 6

In conclusion, we have demonstrated highly diastereoselective reductions of β -substituted and α,β -disubstituted γ -keto amides. Starting with the diastereomerically pure products, γ -hydroxy amides, diastereodivergent synthesis of γ -butyrolactones with contiguous chiral centers was also demonstrated.

EXPERIMENTAL

Melting points were recorded on MITAMURA RIKEN Model 7-12 melting point apparatus. IR spectra were recorded on a HITACHI 260-50 spectrophotometer and recorded in wave number (cm^{-1}). ^1H and ^{13}C NMR spectra were taken on a BRUKER AMX400WB (400 MHz) with CDCl_3 as solvent. Chemical shifts are reported in parts per million (δ value) down field shift from Me_4Si ($\delta = 0$ ppm) or residual CHCl_3 ($\delta = 7.26$ ppm for ^1H or 77.0 ppm for ^{13}C) as internal standard unless otherwise noted. Signal patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. Coupling constants (J) are given in Hertz. Flash chromatography was performed with WAKO C-300 silica gel. Analytical thin layer chromatography was performed on Merck silica plates with F-254 indicator. Analytical high performance liquid chromatography (HPLC) was performed on SHIMADZU SCL-10A solvent delivery systems equipped with CR-4A variable wavelength detector operated 222 nm and a column of Waters N 21018. High resolution MS spectra were taken on a JEOL JMS DX-300. Et_2O , dioxane, and THF were dried and distilled from sodium metal / benzophenone ketyl. CH_2Cl_2 and MeCN were distilled from CaH_2 and stored over 4 Å sieves. All reactions sensitive to oxygen or moisture were conducted under an argon atmosphere in flame dried flasks.

***N,N*-Diisopropyl-3-methyl-4-oxo-4-phenylbutanamide (3a):** To a suspension of activated zinc¹⁷ (392 mg, 6 mmol) in dioxane (1.7 mL) was added 1,2-dibromoethane (43 μL , 0.5 mmol). The mixture was heated at 65°C for 5 min and then cooled to rt. Me_3SiCl (51 μL , 0.4 mmol) was added and stirring was

continued for 15 min. To the mixture was added *N,N*-diisopropyl-3-iodobutanamide (1.49 g, 5 mmol) in dry dioxane (2.5 mL). Heating at 45°C was continued until the iodide was consumed (3.5-4 h). To the mixture were added a solution of Pd₂(dba)₃•CHCl₃ (65 mg, 0.063 mmol) and (*o*-tolyl)₃P (153 mg, 0.5 mmol) in dry dioxane (5 mL), which was stirred for 20 min at rt, and benzoyl chloride (410 μL, 3.5 mmol). The mixture was stirred at rt for 15 h and then was filtered through a short pad of celite. Extraction with AcOEt, concentration, and purification by flash column chromatography (hexane:AcOEt=10:1) gave **3a** (760 mg, 78%). Recrystallization from hexane gave white crystals (mp 78-85°C). ¹H-NMR: δ 1.19-1.38 (m, 15H), 2.38 (dd, J=15.9, 5.4 Hz, 1H), 2.38 (dd, J=15.9, 8.1 Hz, 1H), 3.48 (br s, 1H), 4.06-4.16 (m, 2H), 7.43-7.55 (m, 3H), 8.02-8.04 (m, 2H); IR (KBr): 1680, 1635 (C=O) cm⁻¹; HRMS calcd for C₁₇H₂₅NO₂ (M+) 275.1884, found 275.1880. *Anal.* Calcd for C₁₇H₂₅NO₂: C, 74.20; H, 9.16; N, 5.09. Found: C, 74.22; H, 9.25; N, 4.97.

***N,N*-Diisopropyl-4-(4-chlorophenyl)-3-methyl-4-oxobutanamide (3b)**: 89 %; mp 96-98 °C (hexane); ¹H-NMR: δ 1.17-1.34 (m, 15H), 2.39 (dd, J=15.9, 5.0 Hz, 1H), 2.98 (dd, J=15.9, 8.6 Hz, 1H), 3.48 (br s, 1H), 4.00-4.10 (m, 2H), 7.43 (d, J=8.6 Hz, 2H), 7.97 (d, J=8.6 Hz, 2H); IR (KBr): 1690, 1635 (C=O) cm⁻¹; HRMS calcd for C₁₇H₂₄NO₂Cl (M+) 309.1494, found 309.1494. *Anal.* Calcd for C₁₇H₂₄NO₂Cl: C, 66.05; H, 7.82; N, 4.53. Found: C, 65.88; H, 7.88; N, 4.48.

***N,N*-Diisopropyl-4-(4-methoxyphenyl)-3-methyl-4-oxobutanamide (3c)**: 87 %; mp 71-73°C (hexane); ¹H-NMR: δ 1.18-1.36 (m, 15H), 2.37 (dd, J=15.8, 5.7 Hz, 1H), 2.94 (dd, J=15.8, 7.8 Hz, 1H), 3.48 (br s, 1H), 3.86 (s, 3H), 4.04-4.12 (m, 2H), 6.93 (d, J=8.9 Hz, 2H), 8.02 (d, J=8.9 Hz, 2H); IR (KBr) : 1680, 1640 (C=O) cm⁻¹; HRMS calcd for C₁₈H₂₇NO₃ (M+) 305.1989, found 305.1988. *Anal.* Calcd for C₁₈H₂₇NO₃: C, 70.84; H, 8.92; N, 4.59. Found: C, 70.96; H, 8.98; N, 4.68.

***N,N*-Diisopropyl-3-methyl-5-phenyl-4-oxopentanamide (3d)**: 62 %; oil; ¹H-NMR: δ 1.05 (d, J=7.2 Hz, 3H), 1.15-1.21 (m, 6H), 1.32-1.38 (m, 6H), 2.26 (dd, J=15.5, 4.2 Hz, 1H), 2.82 (dd, J=15.5, 9.3 Hz, 1H), 3.25-3.30 (m, 1H), 3.46 (br s, 1H), 3.93 (s, 2H), 3.98-3.99 (m, 1H), 7.22-7.31 (m, 5H); IR (NaCl): 1715, 1635 (C=O) cm⁻¹; HRMS calcd for C₁₈H₂₇NO₂ (M+) 289.2040, found 289.2045.

Reduction of 3 with DIBAH.

To a precooled (-78 °C) solution of **3** (0.2 mmol) in dry THF (4 mL) was added a toluene solution of DIBAH (0.5 mmol) and the mixture was stirred for 10 min at that temperature. After addition of acetone (3 mL), the mixture was warmed to rt. Usual workup and purification by flash column chromatography on silica gel furnished *syn*-**4**.

(3*R,4*S**)-*N,N*-Diisopropyl-4-hydroxy-3-methyl-4-phenylbutanamide (*syn*-**4a**)**: Oil; ¹H-NMR: δ 0.87-1.44 (m, 15H), 2.18-2.28 (m, 2H), 2.46-2.52 (m, 1H), 3.47 (br s, 1H), 3.85-3.92 (m, 1H), 4.72 (s, 1H), 7.20-7.33 (m, 5H); IR (NaCl): 3360 (OH), 1620 (C=O) cm⁻¹; HRMS calcd for C₁₇H₂₇NO₂ (M+) 277.2040, found 277.2046.

(3*R,4*S**)-*N,N*-Diisopropyl-4-(*p*-chlorophenyl)-4-hydroxy-3-methylbutanamide (*syn*-**4b**)**: mp 90-92°C (hexane); ¹H-NMR: δ 0.85-1.43 (m, 15H), 2.23-2.33 (m, 2H), 2.43-2.53 (m, 1H), 3.49 (br s, 1H), 3.87-3.96 (m, 1H), 4.71 (s, 1H), 7.21-7.29 (m, 4H); IR (KBr): 3370 (OH), 1615 (C=O) cm⁻¹; HRMS calcd for C₁₇H₂₆NO₂Cl (M+) 311.1651 found 311.1647. *Anal.* Calcd for C₁₇H₂₆NO₂Cl: C, 65.62; H, 8.42; N, 4.50. Found: C, 65.61; H, 8.44; N, 4.50.

(3R*,4S*)-N,N-Diisopropyl-4-hydroxy-4-(p-methoxyphenyl)-3-methylbutanamide (*syn-4c*):

Oil; $^1\text{H-NMR}$: δ 0.84-1.43 (m, 15H), 2.03-2.32 (m, 2H), 2.45 (m, 1H), 3.48 (br s, 1H), 3.79 (s, 3H), 3.88-3.91 (m, 1H), 4.66 (s, 1H), 6.85 (d, $J=8.7$ Hz, 2H), 7.21 (d, $J=8.7$ Hz, 2H); IR (NaCl): 3375 (OH), 1615 (C=O) cm^{-1} ; HRMS calcd for $\text{C}_{18}\text{H}_{29}\text{NO}_3$ (M+) 307.2146, found 307.2169.

(3R*,4R*)-N,N-Diisopropyl-3-methyl-4-hydroxy-5-phenylpentanamide (*syn-4d*): Oil; $^1\text{H-NMR}$: δ 1.02 (d, $J=6.9$ Hz, 3H), 1.16 (d, $J=6.7$ Hz, 6H), 1.38 (d, $J=6.7$ Hz, 6H), 2.70-2.09 (m, 1H), 2.30-2.35 (m, 1H), 2.43-2.49 (m, 1H), 2.73-2.80 (m, 2H), 3.45 (br s, 1H), 3.85-3.89 (m, 1H), 3.93-3.96 (m, 1H), 7.18-7.31 (m, 5H); IR (NaCl): 3400 (OH), 1620 (C=O) cm^{-1} ; HRMS calcd for $\text{C}_{18}\text{H}_{29}\text{NO}_2$ (M+) 291.2197, found 291.2187.

General lactonization procedure.

To a precooled (0°C) solution of *syn-4* (0.4 mmol) and triethylamine (202 mg, 2.0 mmol) in dry CH_2Cl_2 (8 mL) was added MsCl (115 mg, 1.0 mmol) and the mixture was stirred at 0°C for 0.5 h. To the reaction mixture was added 4 g of silica gel at rt. After 36 h, elution with AcOEt and purification by TLC gave *trans-5*. The structure was assigned by analogy with **5a**.¹⁸

trans-3-Methyl-4-phenylbutan-4-olide (trans-5a): Oil; $^1\text{H-NMR}$: δ 1.20 (d, $J=6.6$ Hz, 3H), 2.34 (dd, $J=16.9, 10.4$ Hz, 1H), 2.45-2.53 (m, 1H), 2.80 (dd, $J=16.9, 7.7$ Hz, 1H), 4.94 (d, $J=8.3$ Hz, 1H), 7.26-7.26-7.40 (m, 5H); IR (NaCl): 1790 (C=O) cm^{-1} ; HRMS calcd for $\text{C}_{11}\text{H}_{12}\text{O}_2$ (M+) 176.0837, found 176.0831.

trans-4-(p-Chlorophenyl)-3-methylbutan-4-olide (trans-5b): mp $52\sim 54^\circ\text{C}$ (hexane); $^1\text{H-NMR}$: δ 1.19 (d, $J=6.4$ Hz, 3H), 2.35 (dd, $J=16.5, 10.6$ Hz, 1H), 2.44-2.45 (m, 1H), 2.79 (dd, $J=16.5, 7.1$ Hz, 1H), 4.91 (d, $J=8.2$ Hz, 1H), 7.26-7.39 (m, 4H); IR (KBr): 1780 (C=O) cm^{-1} ; HRMS calcd for $\text{C}_{11}\text{H}_{11}\text{O}_2\text{Cl}$ (M+) 210.0447, found 210.0447. *Anal.* Calcd for $\text{C}_{11}\text{H}_{11}\text{O}_2\text{Cl}$: C, 62.90; H, 5.28. Found: C, 62.67; H, 5.52.

trans-4-(p-Methoxyphenyl)-3-methylbutan-4-olide (trans-5c): mp $86\sim 88^\circ\text{C}$ (hexane); $^1\text{H-NMR}$: δ 1.16 (d, $J=6.5$ Hz, 3H), 2.33 (dd, $J=16.9, 10.7$ Hz, 1H), 2.45-2.53 (m, 1H), 2.79 (dd, $J=16.9, 7.5$ Hz, 1H), 3.82 (s, 3H), 4.89 (d, $J=8.6$ Hz, 1H), 6.92 (d, $J=8.6$ Hz, 2H), 7.27 (d, $J=8.6$ Hz, 2H); IR (KBr): 1785 (C=O) cm^{-1} ; HRMS calcd for $\text{C}_{12}\text{H}_{14}\text{O}_3$ (M+) 206.0942, found 206.0943. *Anal.* Calcd for $\text{C}_{12}\text{H}_{14}\text{O}_3$: C, 69.94; H, 6.85. Found: C, 70.06; H, 6.87.

trans-3-Methyl-5-phenylpentan-4-olide (trans-5d): Oil; $^1\text{H-NMR}$: δ 1.06 (d, $J=6.6$ Hz, 3H), 2.15 (dd, $J=17.1, 9.1$ Hz, 1H), 2.24-2.33 (m, 1H), 2.56 (dd, $J=17.1, 8.1$ Hz, 1H), 2.99 (d, $J=5.8$ Hz, 2H), 4.25-4.30 (m, 1H), 7.23-7.33 (m, 5H); IR (NaCl): 1780 (C=O) cm^{-1} ; HRMS calcd for $\text{C}_{12}\text{H}_{14}\text{O}_2$ (M+) 190.0993, found 190.0985.

Ethyl 3-Methyl-4-oxo-4-phenylbutanate (8a): Oil; $^1\text{H-NMR}$: δ 1.20 (t, $J=7.1$ Hz, 3H), 1.23 (d, $J=7.2$ Hz, 3H), 2.45 (dd, $J=16.7, 5.7$ Hz, 1H), 2.96 (dd, $J=16.7, 8.4$ Hz, 1H), 3.93-3.98 (m, 1H), 4.08 (q, $J=7.1$ Hz, 2H), 7.46-8.00 (m, 5H); IR (NaCl): 1730, 1680 (C=O) cm^{-1} ; HRMS calcd for $\text{C}_{13}\text{H}_{16}\text{O}_3$ (M+) 220.1099, found 220.1099.

cis-3-Methyl-4-phenylbutan-4-olide (cis-5a): Oil; $^1\text{H-NMR}$: δ 0.71 (d, $J=7.0$ Hz, 3H), 2.36 (m, 1H), 2.79 (m, 1H), 2.93 (m, 1H), 5.62 (d, $J=6.0$ Hz, 1H), 7.32 (m, 5H); IR (NaCl): 1820 (C=O) cm^{-1} .

Reduction of *syn-3* with $\text{Zn}(\text{BH}_4)_2$.

To a precooled (0°C) solution of *syn-3* (0.2 mmol) in ether (2 mL) was added a solution of Zn(BH₄)₂ in Et₂O (0.34 mmol/mL, 3.0 mL) and the mixture was stirred at that temperature for 4 h. After addition of acetone (1 mL), usual work-up and purification by TLC (hexane:AcOEt=3:1~2:1) gave the corresponding two diastereoisomers in pure forms. Products were confirmed by the comparison with those of authentic samples.¹⁶

Reduction of *syn-3* with L-Selectride.

To a precooled (-78°C) solution of *syn-3* (0.2 mmol) in THF (2 mL) was added L-selectride (750 µL, 0.75 mmol) and the reaction mixture was stirred at -78°C for 3 h. After sequential addition of acetone (1 mL) and 30% H₂O₂ (1 mL), the mixture was left to warm to rt (1 h). Usual work-up and purification by TLC (hexane:AcOEt=3:1~2:1) gave *syn,anti-4* in a pure form. Products were confirmed by the comparison with those of authentic samples.¹⁶

Lactonization under acidic conditions

To a solution of *syn,anti-4* (0.3 mmol) in THF (3 mL) was added CF₃COOH (1 mL) and the mixture was refluxed for 10 h. After removal of the volatiles, purification by TLC (hexane:AcOEt=4:1~3:1) gave *trans,trans-5*.

(2*S,3*S**,4*S**)-2,3-Dimethyl-4-phenylbutan-4-olide (*trans,trans-5e*):** Oil; ¹H-NMR: δ 1.13 (d, J=6.3 Hz, 3H), 1.29 (d, J=7.1 Hz, 3H), 1.96-2.02 (m, 1H), 2.33-2.38 (m, 1H), 4.81 (d, J=10.1 Hz, 1H), 7.32-7.39 (m, 5H); IR (NaCl): 1770, 1710 (C=O) cm⁻¹; HRMS calcd for C₁₂H₁₄O₂ (M+) 190.0993, found 190.0995.

(2*S,3*S**,4*S**)-2,3-Dimethyl-4-tolylbutan-4-olide (*trans,trans-5f*):** mp 58-60 °C (hexane); ¹H-NMR: δ 1.12(d, J=6.3 Hz, 3H), 1.29 (d, J=6.9 Hz, 3H), 1.96-2.00 (m, 1H), 2.30-2.37 (m, 1H), 2.36 (s, 3H), 4.78 (d, J=10.1 Hz, 1H), 7.21 (q, J=8.3 Hz, 4H); IR (NaCl): 1760 (C=O) cm⁻¹; HRMS calcd for C₁₃H₁₆O₂ (M+) 204.1149, found 204.1151. *Anal.* Calcd for C₁₃H₁₆O₂: C, 76.50; H, 7.90. Found: C, 76.12; H, 8.14.

(2*S,3*S**,4*S**)-2,3-Dimethyl-4-(*p*-methoxyphenyl)butan-4-olide (*trans,trans-5g*):** Oil; ¹H-NMR: δ 1.11 (d, J=6.5 Hz, 3H), 1.29 (d, J=6.8 Hz, 3H), 1.96-2.04 (m, 1H), 2.32-2.37 (m, 1H), 3.81 (s, 3H), 4.77 (d, J=10.1 Hz, 1H), 6.91 (d, J=8.5 Hz, 2H), 7.27 (d, J=8.5 Hz, 2H); IR (NaCl): 1760, 1700 (C=O) cm⁻¹; HRMS calcd for C₁₃H₁₆O₃ (M+) 220.1099, found 220.1092.

Lactonization with MsCl.

To a precooled (0°C) solution of *syn,anti-4* (0.2 mmol) and triethylamine (232 mg, 2.3 mmol) in dry CH₂Cl₂ (5 mL) was added MsCl (137 mg, 1.2 mmol) and then the reaction mixture was stirred for 1 h. To the reaction mixture were added silica gel (4.5 g) and AcOEt. After refluxing for 24 h, the product was eluted with AcOEt and purified by TLC to give *trans,cis-5*.

(2*S,3*S**,4*R**)-2,3-Dimethyl-4-phenylbutan-4-olide (*trans,cis-5e*):** Oil; ¹H-NMR: δ 0.76 (d, J=6.7 Hz, 3H), 1.30 (d, J=7.0 Hz, 3H), 2.33-2.37 (m, 1H), 2.49-2.55 (m, 1H), 5.56 (d, J=7.4 Hz, 1H), 7.17-7.40 (m, 5H); IR (NaCl): 1780, 1710 (C=O) cm⁻¹; HRMS calcd for C₁₂H₁₄O₂ (M+) 190.0993, found 190.0992.

(2*S,3*S**,4*R**)-2,3-Dimethyl-4-tolylbutan-4-olide (*trans,cis-5f*):** Oil; ¹H-NMR: δ 0.76 (d, J=7.0 Hz, 3H), 1.29 (d, J=7.1 Hz, 3H), 2.32-2.38 (m, 1H), 2.36 (s, 3H), 2.49-2.52 (m, 1H), 5.52 (d, J=7.8 Hz, 1H),

7.05 (d, J=7.9 Hz, 2H), 7.18 (d, J=7.9 Hz, 2H); IR (NaCl): 1770, 1720 (C=O) cm^{-1} ; HRMS calcd for $\text{C}_{13}\text{H}_{16}\text{O}_2$ (M+) 204.1149, found 204.1157.

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