

High Thermodynamic Diastereoselection in the Equilibration of Acyclic γ -Alkoxy α -Amino Nitriles

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An equilibrium between two diastereomers of an acyclic γ -alkoxy α -amino nitrile was attained in chloroform, and the major component is always its (R^* , S^*)-isomer with high diastereoselectivity.

In acyclic systems, there have been many reports on kinetically controlled 1,3-asymmetric induction, where high stereoselectivity can be realized with aid of metal chelation.¹⁾ On the contrary, high stereoselectivity is unlikely under thermodynamic conditions. Recently we reported a highly selective thermodynamic 1,3-stereocontrol in α -amino nitriles (**1**) derived from α -alkylbenzylamines and aldehydes.²⁾ In this system, the chiral center of the parent α -alkylbenzylamines controls the stereochemical structure of the α -amino nitrile.

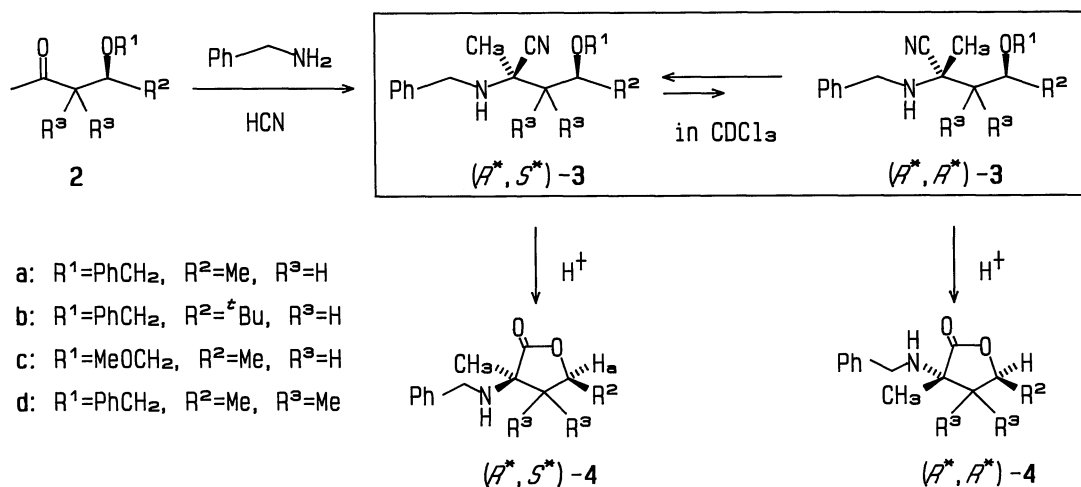
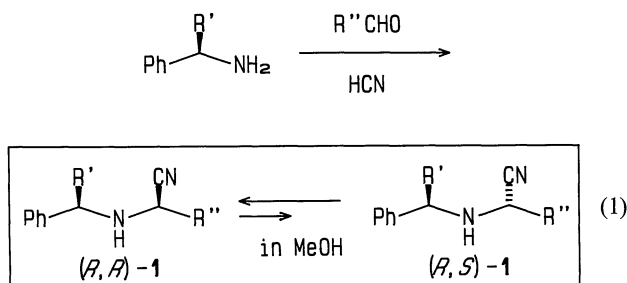
Here we wish to report the second example of high 1,3-asymmetric induction in an acyclic system, i.e., the equilibration between two diastereomeric isomers of an acyclic γ -alkoxy α -amino nitrile (**3**) which, on treatment

with an acid, produces a synthetic precursor of the corresponding γ -hydroxy α -amino acid, i.e. α -methyl α -amino γ -lactone (**4**).

Results and Discussion

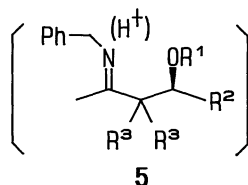
The α -amino nitriles **3a** and **3c** were prepared by the Strecker-type reaction of the corresponding **2** with benzylamine (10 mol equiv), KCN (10 equiv), NaHSO₃ (15 equiv) in water or methanol–water (1:3) at room temperature for ca. 20 h. By the reaction of **2b** with benzylamine hydrochloride (1.0 mol equiv) and KCN (1.1 mol equiv) in water, **3b** was obtained. Under these conditions, insoluble **3** separated out as an oil. Yields of **3a**, **3b**, and **3c** were 64%, 63%, and 76%, respectively. The compound (**3d**) which has two methyl groups at its β -position was synthesized in 55% yield by silylcyanation of the Schiff base derived from **2d** and benzylamine and subsequent hydrolytic desilylation. The product (**3**), which consists of two diastereomers, is so labile that we cannot isolate it in pure form except for a major isomer of **3a**. In chromatographic separation on silica gel or Florisil, **3** decomposed. Recycling high-performance gel permeation chromatography made it possible to isolate **3** in a nearly pure form. Recrystallization of **3a** from hexane afforded (R^* , S^*)-**3a** as colorless crystals.

Equilibration between (R^* , S^*)-**3** and (R^* , R^*)-**3**



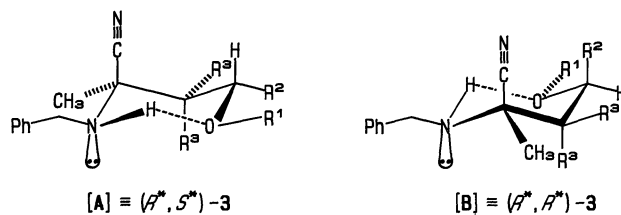
Scheme 1.

occurred in chloroform, probably via the corresponding Schiff base (5) or its protonated form. In methanol, 3 decomposed slowly because 5 reacts with methanol.



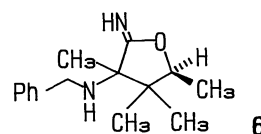
This behavior is in contrast with that of **1**, which does not undergo epimerization in chloroform, but in methanol. When the CDCl_3 solution of pure (R^*, S^*) -**3a** was allowed to stand at room temperature, epimerization took place. After about 1 d, the ratio of (R^*, S^*) -**3a** and (R^*, R^*) -**3a** was 84:16 (^1H NMR). Since this value remained unchanged by elongation of the reaction time, the value of 84:16 was concluded to be the equilibrium ratio of **3a**. The equilibrium ratios of **3b**–**d** were determined after the freshly prepared diastereomeric mixtures were allowed to stand in CDCl_3 for 1 d.³⁾ As summarized in Scheme 2, (R^*, S^*) -**3** is a major component in all cases. Considering that the present 1,3-asymmetric induction is thermodynamically controlled in an acyclic system, the observed concentrations of (R^*, S^*) -**3** are high.

In the IR spectrum of (R^*, S^*) -**3a**, intramolecular hydrogen bonding was observed between the amino hydrogen and the ethereal oxygen. Thus, a dilute CHCl_3 solution (0.013 M, 1 M = 1 mol dm^{-3}) of (R^*, S^*) -**3a** exhibited an IR absorption at 3340 cm^{-1} . Further the lone pair of the amino nitrogen of an α -amino nitrile is widely recognized to be placed antiperiplanar to its cyano group (stereoelectronic effect).^{2,4,5)} Therefore the favorable conformers of (R^*, S^*) -**3** and (R^*, R^*) -**3** are assumed to be [A] and [B], respectively. Since R^2 group is located at equatorial position in [A] and [B] has an axial R^2 group, (R^*, S^*) -**3** is more stable than the corresponding (R^*, R^*) -**3**. The important role of the intramolecular hydrogen bonding in high diastereoselection of **3** is supported by a low equilibrium ratio of (R^*, S^*) -**3a** and (R^*, R^*) -**3a** (66:34) in DMSO. The lower

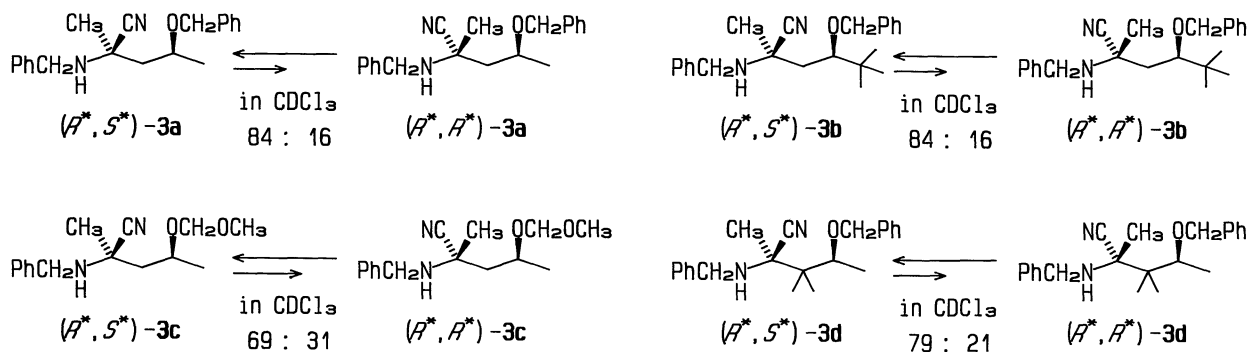


stereoselectivity (69:31) in the equilibration of **3c** is consistent with the decreased electron density of the OR^1 group ($\text{R}^1 = \text{CH}_2\text{OCH}_3$) to make the hydrogen bonding weak.

Finally we describe an acid-catalyzed conversion of **3** into the corresponding α -methyl- α -benzylamino- γ -butyrolactone (**4**) which is brought about by the protonation of the cyano group, the attack of the resulting cation ($-\text{C}=\text{NH}$) on the ethereal oxygen, and the subsequent cleavage of the $\text{R}^1\text{--O}$ bond. The mechanistic consideration indicates that this reaction is stereospecific. Indeed, (R^*, S^*) -**4a** was given as a single isomer in 65% yield when pure (R^*, S^*) -**3a** was treated with 95% sulfuric acid at room temperature for 15 h. On similar treatment of a diastereomeric mixture of **3a** (84:16), the diastereomeric ratio of **4a** was almost unchanged (82:18). Analogously, **3b** (its diastereomeric ratio = 84:16) and **3c** (69:31) also afforded **4b** (75:25) and **4a** (67:33), respectively. In the case of **3d** (79:21), an initial product was 4,5-dihydro-2(3*H*)-furanimine (**6**) (68% yield; 74:26) which was transformed into a 74:26 mixture (96% yield) of (R^*, S^*) -**4d** and (R^*, R^*) -**4d** with *p*-toluenesulfonic acid (PTS) in wet THF. In ^1H NMR spectrum of



(R^*, S^*) -**4**, strong NOE was observed between methine proton (H_a) and α -methyl protons (**4a** ca. 4%; **4b** 4.8%; **4d** 3.6%), whereas no NOE was detected in those of (R^*, R^*) -



Scheme 2.

4. These facts did not determine only the configurations of **4**, but also those of **3**.

In conclusion, thermodynamically controlled acyclic 1,3-asymmetric induction with high efficiency was realized in the equilibration between two diastereomers of **3**. The conversion of **3** to **4** shows that the present asymmetric induction provides a tool for preparing optically active α -amino acids bearing γ -hydroxy and α -methyl groups from easily available optically active 4-alkoxy-2-alkanones.^{6,7)}

Experimental

General Procedures. Melting points were determined on a hot-stage microscope apparatus (Yanagimoto) and are uncorrected. ¹H NMR spectra were obtained on Hitachi R-600 (60 MHz), JEOL JNM-FX 270 (270 MHz) and JEOL JNM-GSX 500 (500 MHz) spectrometers. Chemical shifts are reported in ppm down field from TMS as the internal standard (δ scale). Infrared spectra were determined with a JASCO A-200 spectrometer and data are presented in cm^{-1} for important diagnostic absorptions. Mass spectra (MS) were determined on a Hitachi RMU-7M spectrometer at 70 eV. Microanalytical data were provided by the Analysis Center of Chiba University.

Preparation of β -Alkoxy Ketones (2**).** 4-Benzyloxy-2-pentanone (**2a**) and 4-benzyloxy-5,5-dimethyl-2-hexanone (**2b**) were prepared by the "Moffatt-Pfitzner" oxidation⁸⁾ of the corresponding alcohols with pyridine, trifluoroacetic acid, and dicyclohexylcarbodiimide in dimethyl sulfoxide.

2a: A colorless oil; bp 103–105°C/133 Pa; ¹H NMR (CDCl_3 ; 60 MHz) δ =7.31 (s, 5H), 4.60 (d, 1H, J =12 Hz), 4.45 (d, 1H, J =12 Hz), 4.06 (m, 1H), 2.72 (dd, 1H, J =16, 7 Hz), 2.47 (dd, 1H, J =16, 6 Hz), 2.12 (s, 3H), and 1.25 (d, 3H, J =6 Hz); IR (neat) 1715 cm^{-1} . Found: m/z 192.1160. Calcd for $\text{C}_{12}\text{H}_{16}\text{O}_2$: M, 192.1150.

2b: A colorless oil; bp 117°C/200 Pa; ¹H NMR (CDCl_3 , 270 MHz) δ =7.35–7.21 (m, 5H), 4.58 (d, 1H, J =11.2 Hz), 4.52 (d, 1H, J =11.2 Hz), 3.71 (dd, 1H, J =3.3, 7.9 Hz), 2.69 (dd, 1H, J =7.9, 16.5 Hz), 2.57 (dd, 1H, J =3.3, 16.5 Hz), 2.17 (s, 3H), and 0.94 (s, 9H); IR (neat) 1720 cm^{-1} . Found: C, 77.05; H, 9.47%. Calcd for $\text{C}_{15}\text{H}_{22}\text{O}_2$: C, 76.88; H, 9.46%. Found: m/z 234.1623. Calcd for $\text{C}_{15}\text{H}_{22}\text{O}_2$: M, 234.1618.

4-Methoxymethyl-2-pentanone (**2c**) was prepared by methoxymethylation of 4-hydroxy-2-pentanone with chloromethyl methyl ether and $i\text{-Pr}_2\text{NEt}$.⁹⁾

Hydrolysis of 2-(1,1-dimethyl-2-benzyloxypropyl)-2-methyl-1,3-dioxolane, which was prepared by addition of methyl-lithium to 2-(1-formyl-1-methylethyl)-2-methyl-1,3-dioxolane¹⁰⁾ and subsequent benzylation with benzyl bromide and NaH, gave 4-benzyloxy-3,3-dimethyl-2-pentanone (**2d**): A colorless liquid; ¹H NMR (CDCl_3 , 270 MHz) δ =7.36–7.23 (m, 5H), 4.61 (d, 1H, J =11.5 Hz), 4.36 (d, 1H, J =11.5 Hz), 3.76 (q, 1H, J =6.3 Hz), 2.12 (s, 3H), 1.16 (s, 3H), 1.13 (d, 3H, J =6.3 Hz), and 1.07 (s, 3H); IR (neat) 1700 cm^{-1} . Found: C, 76.50; H, 9.19%. Anal. Calcd for $\text{C}_{14}\text{H}_{20}\text{O}_2$: C, 76.33; H, 9.15%.

Preparation of 2-Benzylamino-4-benzyloxy-2-methylpentanenitrile (3a**) and Its Lactonization.** A Typical Procedure: To a suspension of **2a** (384 mg, 2.00 mmol) in water (30 ml) were added NaHSO_3 (3.12 g, 30.0 mmol), KCN (1.30 g, 20.0 mmol) and a solution of benzylamine (2.12 g, 20.0 mmol) in MeOH

(10 ml) under cooling with ice. After the reaction mixture was stirred at room temperature for 20 h, a deposited oil was extracted with CH_2Cl_2 (30 ml $\times$ 1, 10 ml $\times$ 2). The combined organic layers were dried (MgSO_4) and evaporated in vacuo. After quick chromatography (within 10 min) on silica gel [hexane–ethyl acetate (5:1)], HPLC separation¹¹⁾ afforded a colorless oil (393 mg, 64%) which was shown by ¹H NMR to consist of (R^*,S^*)-**3a** (84%), (R^*,R^*)-**3a** (16%), and **2a** (trace). The major diastereomer was isolated in a pure form by recrystallization from hexane.

(R^*,S^*)-**3a**: Colorless crystals; mp 35.5°C (hexane); ¹H NMR (CDCl_3 , 270 MHz) δ =7.36–7.07 (m, 10H), 4.61 (d, 1H, J =10.6 Hz), 4.40 (d, 1H, J =10.9 Hz), 4.18 (m, 1H), 3.80 (d, 1H, J =12.0 Hz), 3.73 (d, 1H, J =12.0 Hz), 3.11 (br s, 1H, NH), 2.03 (dd, 1H, J =14.5, 10.6 Hz), 1.81 (dd, 1H, J =14.5, 2.6 Hz), 1.48 (s, 3H), and 1.27 (d, 3H, J =5.9 Hz); IR (KBr) 3350 and 2220 cm^{-1} . Found: C, 77.85; H, 7.98; N, 9.10%. Calcd for $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}$: C, 77.98; H, 7.84; N, 9.08%.

¹H NMR of (R^*,R^*)-**3a** ($\text{CDCl}_3\text{-D}_2\text{O}$, 270 MHz), which was assigned from spectra of the diastereomeric mixture: δ =7.36–7.07 (m, 5H), 4.61 (d, 1H, J =11.2 Hz), 4.43 (d, 1H, J =11.2 Hz), 3.88 (m, 1H), 3.86 (s, 2H), 2.08 (dd, 1H, J =9.2, 14.5 Hz), 1.85 (dd, 1H, J =3.3, 14.5 Hz), 1.55 (s, 3H), and 1.30 (d, 3H, J =6.3 Hz).

A diastereomeric mixture (84:16) of **3a** (376 mg, 1.22 mmol) was added to concd sulfuric acid (95%, 5.0 ml) under cooling with ice. After being stirred for 15 h at room temperature, the resulting mixture was poured onto ice containing aqueous NH_3 (28% concn; 15 ml). After extraction with CH_2Cl_2 (30 ml $\times$ 1, 10 ml $\times$ 2), the combined organic layers were dried (MgSO_4), evaporated in vacuo, and subjected to flash chromatography on silica gel [hexane–ethyl acetate (7:2–2:1)] to give (R^*,S^*)-**4a** (101 mg, 38%) and (R^*,R^*)-**4a** (22.0 mg, 8.2%).

(R^*,S^*)-**4a**: A colorless oil; ¹H NMR (500 MHz, CDCl_3) δ =7.37–7.24 (m, 5H), 4.53 (qt, 1H, J =5.9, 10.1 Hz), 3.80 (d, 1H, J =12.1 Hz), 3.68 (d, 1H, J =12.1 Hz), 2.19 (dd, 1H, J =5.9, 13.0 Hz), 2.06 (dd, 1H, J =10.1, 13.0 Hz), 1.72 (br s, 1H, NH), 1.45 (d, 3H, J =6.0 Hz), and 1.43 (s, 3H); IR (neat) 3340 and 1770 cm^{-1} . Found: C, 71.16; H, 7.84; N, 6.39%. Calcd for $\text{C}_{13}\text{H}_{17}\text{NO}_2$: C, 71.21; H, 7.81; N, 6.39%.

(R^*,R^*)-**4a**: Colorless crystals; mp 39–40°C (hexane– Et_2O); ¹H NMR (CDCl_3 , 500 MHz) δ =7.33–7.24 (m, 5H), 4.70 (qt, 1H, J =6.3, 8.5 Hz), 3.89 (d, 1H, J =12.1 Hz), 3.74 (d, 1H, J =12.1 Hz), 2.47 (dd, 1H, J =6.6, 13.5 Hz), 1.80 (dd, 1H, J =8.5, 13.5 Hz), 1.49 (br s, 1H, NH), 1.47 (s, 3H), and 1.42 (d, 3H, J =6.3 Hz); IR (KBr) 3290 and 1750 cm^{-1} . Found: C, 71.26; H, 7.85; N, 6.36%. Calcd for $\text{C}_{13}\text{H}_{17}\text{NO}_2$: C, 71.21; H, 7.81; N, 6.39%.

Similarly, treatment of pure (R^*,S^*)-**3a** (110 mg, 0.357 mmol) with sulfuric acid gave (R^*,S^*)-**4a** (51.1 mg, 65%). In this reaction mixture, we could not detect (R^*,S^*)-**4a**.

2-Benzylamino-4-methoxymethoxy-2-methylbutanenitrile (3c**) and Its Lactonization:** In a similar manner, **3c** (418 mg, 76%) was obtained from **2c** (292 mg, 2.00 mmol) as a colorless oil, which was shown by ¹H NMR to consist of (R^*,S^*)-**3c** (66%), (R^*,R^*)-**3c** (30%), and **2c** (4%): ¹H NMR (CDCl_3 , 270 MHz) δ =7.41–7.23 (m, 5H), 4.71 (d, 0.30 $\times$ 1H, J =7.3 Hz), 4.70 (d, 0.66 $\times$ 1H, J =6.9 Hz), 4.65 (d, 0.30 $\times$ 1H, J =7.3 Hz), 4.63 (d, 0.66 $\times$ 1H, J =6.9 Hz), 4.20 (m, 0.66 $\times$ 1H), 4.01 (m, 0.30 $\times$ 1H), 3.88 (br m, 0.96 $\times$ 2H), 3.352 (s, 0.30 $\times$ 3H), 3.345 (s, 0.04 $\times$ 3H), 3.32 (s, 0.66 $\times$ 3H), 2.83 (br s, 0.96 $\times$ 1H, NH), 2.18 (s, 0.04 $\times$ 3H), 2.06 (dd, 0.30 $\times$ 1H, J =5.3, 14.8 Hz), 2.00 (dd, 0.66 $\times$ 1H, J =7.9,

14.5 Hz), 1.82 (dd, 0.30×1H, $J=3.6$, 14.5 Hz), 1.78 (dd, 0.66×1H, $J=2.7$, 14.5 Hz), 1.57 (s, 0.30×3H), 1.50 (s, 0.66×3H), 1.26 (d, 0.30×3H, $J=6.3$ Hz), 1.24 (d, 0.66×3H, $J=5.9$ Hz), and 1.22 (d, 0.04×3H, $J=6.3$ Hz); IR (neat) 3350 and 2220 cm^{-1} .

When a 69:31 mixture of (R^* , S^*)- and (R^* , R^*)-**3c** was treated with sulfuric acid, a 67:33 mixture of (R^* , S^*)- and (R^* , R^*)-**4a** was given in 37% yield.

2-Benzylamino-4-benzoyloxy-2,5,5-trimethylhexanenitrile (3b) and 2-Benzylamino-4-(*t*-butyl)-2-methyl- γ -butyrolactone (4b): To a stirring suspension of **2b** (234 mg, 1.00 mmol) in water (0.50 ml) were added benzylamine hydrochloride (145 mg, 1.01 mmol) and KCN (72.0 mg, 1.11 mmol) at room temperature. After the reaction mixture was stirred at the same temperature for 20 h, CH_2Cl_2 (20 ml) and anhydrous MgSO_4 to remove the water were added, and the solvent was evaporated in vacuo. A short-column chromatography on silica gel (eluent: ethyl acetate) followed by HPLC separation¹¹⁾ afforded a colorless oil (229 mg, 63%) which was shown by ^1H NMR to consist of (R^* , S^*)-**3b** (84%) and (R^* , R^*)-**3b** (16%); ^1H NMR (CDCl_3 , 270 MHz) $\delta=7.37\text{--}7.03$ (m, 10H, ArH), 4.82 (d, 0.84×1H, $J=11.2$ Hz, OCH_2Ph), 4.78 (d, 0.84×1H, $J=11.5$ Hz, OCH_2Ph), 3.91 (d, 0.16×1H, $J=9.6$ Hz, NCH_2Ph), 3.90 (d, 0.16×1H, $J=9.6$ Hz, NCH_2Ph), 3.74 (br s, 0.84×2H, NCH_2Ph), 3.68 (dd, 0.84×1H, $J=3.3$, 10.2 Hz, OCHCH_2), 3.37 (dd, 0.16×1H, $J=3.6$, 6.9 Hz, OCHCH_2), 1.98 (dd, 0.84×1H, $J=10.2$, 14.5 Hz, OCHCH_2), 1.88 (dd, 0.84×1H, $J=3.3$, 14.5 Hz), 1.57 (s, 0.16×3H, CH_3CCN), 1.50 (s, 0.84×3H, CH_3CCN), 0.99 (s, 0.84×9H, $\text{C}(\text{CH}_3)_3$), and 0.98 (s, 0.84×9H, $\text{C}(\text{CH}_3)_3$); IR (neat) 3340 cm^{-1} .

Treatment of thus obtained **3b** with sulfuric acid resulted in formation of **4b** with a diastereomeric ratio of 75:25 in 51% yield.

(R^* , S^*)-**4b**: Colorless crystals; mp 74°C (hexane); ^1H NMR (CDCl_3 , 500 MHz) $\delta=7.38\text{--}7.24$ (m, 5H), 4.10 (dd, 1H, $J=6.1$, 11.0 Hz), 3.78 (d, 1H, $J=12.1$ Hz), 3.68 (d, 1H, $J=12.1$ Hz), 2.24 (dd, 1H, $J=11.0$, 12.9 Hz), 1.92 (dd, 1H, $J=6.1$ Hz, 12.9 Hz), 1.76 (br s, 1H, NH), 1.44 (s, 3H), 0.97 (s, 9H); IR (KBr) 3340, 1760 cm^{-1} . Found: C, 73.75; H, 8.94; N, 5.23%. Calcd for $\text{C}_{16}\text{H}_{23}\text{NO}_2$: C, 73.53; H, 8.87; N, 5.36%. Found: m/z 217.1837. Calcd for $\text{C}_{15}\text{H}_{23}\text{N}$: $\text{M}-\text{CO}_2$, 217.1829.

(R^* , R^*)-**4b**: Colorless crystals; mp 78°C (hexane); ^1H NMR (CDCl_3 , 500 MHz) $\delta=7.35\text{--}7.24$ (m, 5H), 4.28 (dd, 1H, $J=6.6$, 9.9 Hz), 3.80 (d, 1H, $J=12.1$ Hz), 3.76 (d, 1H, $J=12.1$ Hz), 2.18 (dd, 1H, $J=6.6$, 13.8 Hz), 1.95 (dd, 1H, $J=9.9$, 13.8 Hz), 1.55 (br s, 1H, NH), 1.45 (s, 3H) and 0.94 (s, 9H); IR (KBr) 3340 and 1740 cm^{-1} . Found: C, 73.46; H, 8.93; N, 5.17%. Calcd for $\text{C}_{16}\text{H}_{23}\text{NO}_2$: C, 73.53; H, 8.87; N, 5.36%. Found: m/z 217.1837. Calcd for $\text{C}_{15}\text{H}_{23}\text{N}$: $\text{M}-\text{CO}_2$, 217.1829.

2-Benzylamino-4-benzoyloxy-2,3,3-trimethylpentanenitrile (3d): The mixture of **2d** (440 mg, 2.00 mmol), benzylamine (856 mg, 8.00 mmol), and $\text{BF}_3\cdot\text{OEt}_2$ (20 mg) was stirred at 80°C for 16 h under an atmosphere of nitrogen. After removal of the unreacted benzylamine under reduced pressure (100°C/67 Pa), the residue was dissolved in CH_2Cl_2 (6.0 ml) and then trimethylsilyl cyanide (0.40 ml, 3.0 mmol) and ZnCl_2 (20 mg) were added at room temperature. After being stirred at the same temperature for 4 h, the reaction mixture was passed through a short column on silica gel (5 g) using Et_2O as an eluent. Purification by recycling HPLC¹¹⁾ gave a colorless oil (504 mg) which was shown by ^1H NMR to comprise (R^* , S^*)-**3d** (63%), (R^* , R^*)-**3d** (17%), and the Schiff base (**5**; $\text{R}^1=\text{PhCH}_2$, $\text{R}^2=\text{R}^3=\text{Me}$) (20%) which might be produced from **3d** by

elimination of a HCN moiety during workup. The yield of **3d** was calculated to be 55%. ^1H NMR of **3d** (CDCl_3 , 270 MHz): $\delta=7.36\text{--}7.03$ (m, 10H), 4.623 (d, 0.20×1H, $J=11.9$ Hz), 4.617 (d, 0.17×1H, $J=11.5$ Hz), 4.60 (d, 0.63×1H, $J=10.6$ Hz), 4.51 (br s, 0.20×2H, NCH_2Ph), 4.42 (d, 0.63×1H, $J=10.5$ Hz, OCH_2Ph), 4.37 (d, 0.20×1H, $J=11.9$ Hz, OCH_2Ph), 4.29 (d, 0.17×1H, $J=11.5$ Hz, OCH_2Ph), 3.98 (q, 0.63×1H, $J=6.3$ Hz, OCHCH_3), 3.82 (br s, 0.17×2H, NCH_2Ph), 3.74 (d, 0.63×2H, $J=6.3$ Hz, NCH_2Ph), 3.74 (q, 0.20×1H, $J=6.3$ Hz, OCHCH_3), 3.57 (q, 0.17×1H, $J=6.3$ Hz, OCHCH_3), 3.32 (br t, 0.80×1H, $J=6.6$ Hz, NH), 1.84 (s, 0.20×3H), 1.46 (s, 0.17×3H), 1.39 (s, 0.63×3H), 1.30 (d, 0.17×3H, $J=6.3$ Hz), 1.25 (d, 0.63×3H, $J=6.3$ Hz), 1.21 (s, 0.17×3H), 1.19 (s, 0.17×3H), 1.13 (s, 0.20×6H), 1.12 (d, 0.20×3H, $J=6.3$ Hz), 1.03 (s, 0.63×3H), and 1.00 (s, 0.63×3H); IR (neat) 3350 and 2220 cm^{-1} .

3-Benzylamino-3,4,4,5-tetramethyl-4,5-dihydro-2(3H)-furanimine (6): The similar procedure gave 3-benzylamino-3,4,4,5-tetramethyl-4,5-dihydro-2(3H)-furanimine (**6**) as a diastereomeric mixture (200 mg, 68%; (R^* , S^*):(R^* , R^*)=79:21) from the equilibrium mixture of (R^* , S^*)-**3d** and (R^* , R^*)-**3d** (504 mg, 80% purity, 1.20 mmol). **6** was colorless crystals; mp 67–71°C; ^1H NMR (CDCl_3 , 270 MHz) $\delta=7.41\text{--}7.21$ (m, 5H, ArH), 4.63 (q, 0.26×1H, $J=6.6$ Hz, OCHCH_3), 4.14 (q, 0.74×1H, $J=6.3$ Hz, OCHCH_3), 4.04 (d, 0.74×1H, $J=12.5$ Hz, NCH_2Ph), 3.85 (d, 0.74×1H, $J=12.2$ Hz, NCH_2Ph), 3.83 (s, 0.26×2H, NCH_2Ph), 1.40 (s, 0.74×3H, NCCCH_3), 1.27 (s, 0.26×3H, NCCCH_3), 1.24 (d, 0.74×3H, $J=6.6$ Hz, OCHCH_3), 1.20 (d, 0.26×3H, $J=6.6$ Hz, OCHCH_3), 1.10 (s, 0.74×3H, $\text{C}(\text{CH}_3)_2$), 0.95 (s, 0.74×3H, $\text{C}(\text{CH}_3)_2$), 0.94 (s, 0.26×3H, $\text{C}(\text{CH}_3)_2$), and 0.85 (s, 0.26×3H, $\text{C}(\text{CH}_3)_2$); IR (KBr) 3340, 3290, and 1675 cm^{-1} . Found: C, 73.26; H, 9.02; N, 11.36%. Calcd for $\text{C}_{15}\text{H}_{22}\text{N}_2\text{O}$: C, 73.13; H, 9.00; N, 11.37%.

2-Benzylamino-2,3,3,4-tetramethyl- γ -butyrolactone (4d): To the solution of **6** (269 mg, 1.09 mmol) in THF (8 ml) were added *p*-toluenesulfonic acid monohydrate (560 mg, 2.95 mmol) and H_2O (0.8 ml). After reflux for 16 h, the reaction mixture was neutralized with saturated aqueous NaHCO_3 and extracted with Et_2O (40 ml). The organic layer was washed with brine, dried (MgSO_4), and evaporated in vacuo. Flash chromatography on silica gel [hexane–ethyl acetate (5:1)] afforded a 74:26 mixture (R^* , S^*)-**4d** and (R^* , R^*)-**4d** (258 mg, 96% yield), which was separated by recycling HPLC¹²⁾ [eluent: hexane–ethyl acetate (2:1)].

(R^* , S^*)-**4d**: Colorless crystals; mp 60–61°C; ^1H NMR (CDCl_3 , 500 MHz) $\delta=7.40\text{--}7.23$ (m, 5H), 4.25 (q, 1H, $J=6.4$ Hz), 4.13 (d, 1H, $J=12.3$ Hz), 3.82 (br d, 1H, $J=11.5$ Hz), 1.40 (s, 3H), 1.29 (d, 3H, $J=6.6$ Hz), 1.05 (s, 3H), and 0.99 (s, 3H); IR (KBr) 3320 and 1760 cm^{-1} . Found: C, 72.96; H, 8.62; N, 5.58%. Calcd for $\text{C}_{15}\text{H}_{21}\text{N}_2\text{O}_2$: C, 72.84; H, 8.56; N, 5.66%.

(R^* , R^*)-**4d**: Colorless crystals; mp 49–50°C; ^1H NMR (CDCl_3 , 500 MHz) $\delta=7.33\text{--}7.22$ (m, 5H), 4.71 (q, 1H, $J=6.4$ Hz), 3.87 (d, 1H, $J=12.6$ Hz), 3.71 (d, 1H, $J=12.6$ Hz), 1.26 (d, $J=6.4$ Hz, 3H), 1.25 (s, 3H), 0.97 (s, 3H), and 0.89 (s, 3H); IR (KBr) 3330 and 1760 cm^{-1} . Found: C, 72.83; H, 8.64; N, 5.54%. Calcd for $\text{C}_{15}\text{H}_{21}\text{N}_2\text{O}_2$: C, 72.84; H, 8.56; N, 5.66%.

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11) With LC-908 (Japan Analytical Industry, Co., Ltd.) equipped with JAIGEL-1H (i.d. 20×600 mm) and JAIGEL-2H (i.d. 20×600 mm); eluent, 0.5% NEt_3 containing CHCl_3 .

12) With LC-908 (Japan Analytical Industry, Co., Ltd.) equipped with D-SIL-5-06-B (S-5 60A SIL) (i.d. 30×250 mm) (YMC Co., Ltd.).
