An Asymmetric Synthesis of Lactones from Cyclic Acid Anhydrides with Chiral Binaphthyldiamines¹⁾

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Asymmetric ring opening of the cyclic acid anhydrides *cis*-**2**, **3**~**6** with the axially dissymmetric binaphthyldiamines (*S*)-**1a**~**d** and subsequent esterification gave diastereoisomeric mixtures of the amide-esters **7a**~**h**. Successive reduction of the ester group and ring closure by hydrolysis afforded (–)-*cis*-2,4-dimethyl-δ-valerolactone (**8**, 92% *e.e.*), (–)-mevalonolactone (**9**, 58% *e.e.*), (+)-3-isopropyl-δ-valerolactone (**10**, 42% *e.e.*), and (+)-2,3-methylene-γ-butyrolactone (**11**, 46% *e.e.*). Through kinetic resolution of the racemic anhydride *trans*-**2**, (–)-*trans*-2,4-dimethyl-δ-valerolactone (**12**) was yielded in a 74% *e.e.*, whose absolute configuration was established to be 2*R*,4*R*.

Among various types of asymmetric reactions, it is an effective method to prepare optically active products from symmetrical molecules.²⁾ From this viewpoint, dehydrogenases³⁾ and esterases⁴⁾ have been used for the discrimination between enantiotopic groups, and optically active lactones were prepared by subsequent chemical conversion. As a non-enzymatic counterpart, selective acyl-substitution has been successfully performed in which active amides with a chiral leaving group were employed.⁵⁾ Asymmetric syntheses of lactones based on the discrimination have also been effected by chemical oxidation and reduction.⁶⁾

It has been reported that diastereoisomeric mixtures of a half-amide and a half-ester were formed with low selectivity by treating cyclic acid anhydrides with a chiral amine⁷⁾ and a chiral alcohol,⁸⁾ respectively. However, if the selectivity could be improved by choosing appropriate nucleophiles, the reaction might be a promising candidate for enantiotopic group differentiation.⁹⁾ Because an axially dissymmetric structure was considered to be

suitable for the selection, we chose (*S*)-[1,1'-binaphthyl]-2,2'-diamine (**1a**)^{10,11)} as an axially dissymmetric parent compound. We also attempted to elaborate the chiral nucleophile for exhibiting high selectivity through acylation or alkylation of one of the two amino groups in **1a**.

Selective monoacylation of **1a** with trifluoroacetic anhydride provided the trifluoroacetyl derivative **1b** in a 67% yield. The piperidino derivative **1c** was afforded in a 38% yield by reductive *N*-alkylation with glutaraldehyde and sodium cyanoborohydride. A one-pot synthesis through ozonolysis of 2,5-dihydrofuran and subsequent reductive *N*-alkylation gave the morpholino derivative **1d** in a 42% yield.¹²⁾ Taking account of naturally occurring lactones or the analogs, the prochiral acid anhydrides **2**~**6** were subjected to the present asymmetric synthesis.

SCHEME 1. Asymmetric Ring Opening of Cyclic Acid Anhydrides with Chiral Amines.

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SCHEME 2. Chiral Amines, Acid Anhydrides, Amide-esters and Lactones.

The stereoselectivity of the asymmetric ring opening was assessed on the diastereoisomeric ratios of the amide-esters (IV) by HPLC (Scheme 1). A preliminary examination of the selectivity on (IV) revealed that it was not always satisfactory in every combination of the acid anhydrides (I) and the amines (II). However, the selectivity was particularly high in several cases (Table I).

Based on these observations, optically active *cis*-2,4-dimethyl- δ -valerolactone (**8**) was synthesized. An equimolar amount of *cis*-2,4-dimethylglutaric anhydride (*cis*-**2**)¹³ reacted with **1c** to give the half-amide. After treatment with diazomethane, the diastereoisomeric ratio in the resulting amide-ester **7b** was determined by HPLC (Table I, run 2). The amide-ester **7b** was subjected to selective reduction of the ester group by lithium borohydride. Hydrolysis then gave (–)-(2*R*,4*S*)-*cis*-2,4-dimethyl- δ -valerolactone (**8**)¹⁴ in an overall yield of 77% from *cis*-**2**. The optical purity was 92% based on the maximum rotation which coincided with the diastereoisomeric ratio in **7b**. The diastereoisomers of **7a** from *cis*-**2** and **1a** were separated from each other by silica gel chromatography (Table I, run 1). The major isomer of **7a** was *N*-acetylated and then sub-

jected to successive reduction and hydrolysis as earlier mentioned to afford optically pure (–)-**8**.

Stereoselection was moderate in 3-hydroxy-3-methylglutaric anhydride (**3**),¹⁵ 3-isopropylglutaric anhydride (**4**),¹⁶ and 1,2-cyclopropanedicarboxylic anhydride (**5**)¹⁷ (Table I, run 4~7). Successive reduction and hydrolysis of **7e**, **7f** and **7g** as described for **7b** afforded (–)-(R)-mevalonolactone (**9**, 58% *e.e.* run 5), (+)-(R)-3-isopropyl- δ -valerolactone (**10**, 42% *e.e.* run 6) and (+)-(2*R*,3*S*)-2,3-methylene- γ -butyrolactone (**11**, 46% *e.e.* run 7), respectively. Because the rotatory method for determining the enantiomeric excess (*e.e.*) of **9** has been reported to be unreliable,¹⁸ it was determined by using a chiral shift reagent, and was somewhat lower than the value expected from the diastereoisomeric ratio in **7e** (run 5). This may have been due to partial racemization during the isolation process. As expected from the separation factor of **7f** (α =1.22), the chromatographic separation of each diastereoisomer was successfully performed. The stereochemical outcome showed that the pro-*R* carbonyl group was preferentially attacked in the reactions. The selectivity of the reaction with *cis*-1,2-cyclohexane-

TABLE I. ASYMMETRIC SYNTHESIS OF LACTONES THROUGH DIFFERENTIATION BETWEEN ENANTOTOPIC GROUPS OR ENANTIOMERS

Run	Acid anhydride	Amine	Amide-ester			Lactone				
			Compound	Ratio	α^b	Compound	Yield (%)	Config.	$[\alpha]_D$	<i>e.e.</i>
1	<i>cis</i> -2	1a	7a	20:80	1.40 ^c					
2	<i>cis</i> -2	1c	7b	4:96	1.05 ^d	8	77	2 <i>R</i> ,4 <i>S</i>	-37.8 ^{oi}	92
3	<i>cis</i> -2	1d	7c	10:90	1.39 ^e					
4	3	1c	7d	20:80	1.17 ^f					
5	3	1d	7e	17:83	1.16 ^f	9	44	<i>R</i>	-12.2 ^{oj}	58
6	4	1b	7f	79:21 ^a	1.22 ^g	10	38	<i>R</i>	+7.1 ^{ok}	42
7	5	1b	7g	29:71	1.06 ^g	11	65	2 <i>R</i> ,3 <i>S</i>	+28.0 ^{ol}	46
8	6	1a	7h	38:62	1.40 ^c					
9	<i>trans</i> -2	1c	7b	87:13	1.20 ^d	12	47	2 <i>R</i> ,4 <i>R</i>	-60.1 ^o	74
10	<i>trans</i> -2	1d	7c	—	^h	12	41	2 <i>R</i> ,4 <i>R</i>	-53.4 ^o	66

^a This was the best ratio in several experiments and does not coincide with the *e.e.* of **10** that was actually synthesized.

^b Separation factor.

^c Ethyl acetate-hexane-triethylamine = 1:2:0.03, 3 ml/min.

^d Ethyl acetate-hexane-triethylamine = 1:7.5:0.05, 3 ml/min.

^e Ethyl acetate-hexane-triethylamine = 1:4:0.05, 3 ml/min.

^f Hexane-2-propanol-triethylamine = 20:1:0.2, 0.4 ml/min.

^g Ethyl acetate-hexane-triethylamine = 2:3:0.05, 3 ml/min.

^h HPLC separation was incomplete for assessing the ratio.

ⁱ $[\alpha]_{D_{\max}}^{25}$ -41.1° (CHCl₃); C.-S. Chen, Y. Fujimoto and C. J. Sih, *J. Am. Chem. Soc.*, **103**, 3580 (1981).

^j $[\alpha]_{D_{\max}}^{20}$ -23.0° (*c* = 6, EtOH); R. H. Cornforth, J. W. Cornforth and G. Popják, *Tetrahedron*, **18**, 1351 (1962).

^k $[\alpha]_{D_{\max}}^{20}$ +16.9° (*c* = 1.037, EtOH); G. Yabuya and K. Mori, *Nippon Nôgeikagaku Kaishi*, **56**, 1121 (1982).

^l $[\alpha]_{D_{\max}}^{25}$ +61.8° (*c* = 6.6, CHCl₃); I. J. Jakovac, G. Ng, K. P. Lok and J. B. Jones, *J. Chem. Soc., Chem. Commun.*, 515 (1980).

dicarboxylic anhydride (**6**) was low, but chromatographic separation of **7h** was also successful (α = 1.40).

The piperidino derivative **1c** reacted with a five-fold excess of racemic 2,4-dimethylglutaric anhydride (*trans*-2). The stereoselectivity of this kinetic resolution was evaluated on the ratio of **7b** (Table I, run 9).¹⁹ In the same manner as that for the *cis*-isomer **8**, (–)-*trans*-2,4-dimethyl- δ -valerolactone **12** with $[\alpha]_D$ -60.1° was obtained in an overall yield of 47% from **1c**. The *e.e.* of **12** was calculated to be 74% from the diastereoisomeric ratio in **7b**. Using **1d**, **12** with $[\alpha]_D$ -53.4° was also synthesized, whose *e.e.* was determined to be 66% by a comparison of the specific rotations of **12** (run 9, 10). The absolute configuration of (–)-**12** was established by the chiroptical method, a simple comparison of its CD spectrum with those of (–)-**8** and

TABLE II. CD MAXIMA OF THE OPTICALLY ACTIVE 2-METHYLATED δ -VALEROLACTONES

Lactone	$[\alpha]_D$	Ellipticity ^a	
		$[\theta]$ (deg·cm ² ·dmol ⁻¹)	(nm)
2 <i>R</i> ,4 <i>R</i> - 12	-53.4°	-2930	221
2 <i>R</i> ,4 <i>S</i> - 8	-21.8°	-1550	227
2 <i>R</i> - 13 ^b	-40.7°	-3910	225

^a Measured in hexane.

^b The data were reported in the literature. A. I. Meyers, Y. Yamamoto, E. D. Mihelich, and R. A. Bell, *J. Org. Chem.*, **45**, 2792 (1980).

(*R*)-(–)-2-methyl- δ -valerolactone (**13**) suggesting the 2*R*,4*R* configuration of (–)-**12** (Table II). This conclusion was confirmed by the lactone chirality rule which correlated the Cotton effect with the dihedral angle around the ester group.²⁰ The conformation (A) pre-

FIG. 1. ^1H NMR Spectrum (400 MHz) of *trans*-2,4-Dimethyl- δ -valerolactone (**12**) in $\text{CDCl}_3\text{-CCl}_4$ (1:2).

dicted by ^1H NMR spectroscopy (400 MHz, Fig. 1) and the negative maximum at 221 nm in its CD spectrum also indicated the 2*R*,4*R* configuration of (–)-**12**. Accordingly, it was the 2*R*,4*R*-enantiomer of *trans*-**2** that reacted preferentially with **1c** and **1d**.

EXPERIMENTAL

IR spectra were recorded with a Hitachi 215 spectrometer, and ^1H NMR spectra were measured in deuteriochloroform with Varian EM-360 (60 MHz), JEOL FX-100 (100 MHz) and GX-400 (400 MHz) spectrometers. Mass spectra were recorded with a JEOL JMS-DX-300, and optical rotations were measured with a Perkin-Elmer R-241 polarimeter. A Jasco Model J-20 spectropolarimeter was employed for CD spectra. HPLC analyses were carried out on a Jasco BIP-1 chromatograph system equipped with a silica gel column (NUCLEOSIL 50-5, 4 mm $\times$ 25 cm). GLC analysis was performed on a Shimadzu GC-4CM gas chromatograph (4 mm $\times$ 1 m column, 5% XE-60). A Varian Aerograph Model 920 gas chromatograph (1/4" $\times$ 1 m column, 10% SE-30) was used for preparative GLC. (S)-(–)-[1,1'-Binaphthyl]-2,2'-diamine [**1a**] $[\alpha]_{\text{D}}^{25} -151.5^\circ$ ($c=1.47$, pyridine); lit., $[\alpha]_{\text{D}} -149.5^\circ$] was prepared according to the literature.¹⁰⁾

Preparation of the trifluoroacetyl derivative 1b. Trifluoroacetic anhydride (1.62 g, 7.7 mmol) was added to a mixture of **1a** (2.0 g, 7.0 mmol), trifluoroacetic acid (5.4 ml) and CH_2Cl_2 (10 ml) with ice-cooling. The mixture was stirred at room temperature overnight and poured into sat. NaHCO_3 (50 ml). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (50 ml $\times$ 3). The combined extracts were washed with sat. NaCl and dried over anhyd. Na_2SO_4 . After evaporation, the residue was subjected to MPLC (silica gel, 7% EtOAc in hexane) to afford **1b** as an amorphous powder (1.8 g, 67%). $[\alpha]_{\text{D}}^{25} +29.0^\circ$ ($c=0.99$, CHCl_3). Mass m/z : 380 (M^+). IR $\nu_{\text{max}}^{\text{KBr}} \text{ cm}^{-1}$: 3380, 1730, 1620, 1530,

1505, 815, 755. ^1H NMR δ : 3.7 (broad s, 2H, $-\text{NH}_2$), 6.7~8.2 (m, 12H, aromatic protons), 8.50 and 8.66 (2 $\times$ s, 1H, $-\text{NHCO}-$).

Preparation of the piperidino derivative 1c. To a mixture of **1a** (2.0 g, 7.0 mmol), DMF (8 ml) and CH_3CN (25 ml), an aqueous solution of glutaraldehyde (25%, 2.8 ml, 7.0 mmol) and NaBH_3CN (0.44 g, 7.0 mmol) were added with ice-cooling. The mixture was then stirred at room temperature for 2 hr, during which a solution of acetic acid (1.3 g, 21 mmol) in CH_3CN (5 ml) was added portionwise to maintain the pH around 7. After stirring overnight, 3N HCl (50 ml) was added and the acidic solution was washed with ether (30 ml). The aqueous layer was made alkaline with 15% NaOH and extracted with CH_2Cl_2 (50 ml $\times$ 3). The combined extracts were washed with sat. NaCl and dried over anhyd. Na_2SO_4 . After evaporation, the residue was subjected to MPLC (silica gel, 14% EtOAc in hexane) to afford **1c** as an amorphous powder (0.95 g, 38%). $[\alpha]_{\text{D}}^{20} -12.3^\circ$ ($c=1.97$, CHCl_3). Mass m/z : 352 (M^+). IR $\nu_{\text{max}}^{\text{KBr}} \text{ cm}^{-1}$: 3380, 1620, 1505, 810, 750. ^1H NMR δ : 0.9~1.5 (m, 6H, $-\text{CH}_2\text{CH}_2\text{CH}_2-$), 2.8~3.1 (m, 4H, $-\text{N}(\text{CH}_2)_2$), 3.7 (broad s, 2H, $-\text{NH}_2$), 6.9~8.1 (m, 12H, aromatic protons).

Preparation of the morpholino derivative 1d. Ozone gas was passed into a solution of 2,5-dihydrofuran (1.12 g, 16 mmol) in MeOH (25 ml) at -60°C until a blue color developed. The excess ozone was expelled by passing argon gas at -60°C . NaBH_3CN (3.0 g, 48 mmol) and a solution of **1a** (4.3 g, 15 mmol) in DMF (30 ml) were added at -50°C . The mixture was stirred with ice-cooling for 2.5 hr, during which acetic acid (8.6 g, 0.14 mol) was added portionwise to maintain the pH around 7. After evaporation, 5% NaOH (50 ml) was added and the mixture was extracted with CH_2Cl_2 (50 ml $\times$ 3). The combined extracts were washed with sat. NaCl and dried over anhyd. Na_2SO_4 . After evaporation, the residue was subjected to MPLC (silica gel, 3% 2-propanol in hexane) to afford **1d** as an amorphous powder (2.3 g, 42%). $[\alpha]_{\text{D}}^{20} -53.3^\circ$ ($c=1.1$, CHCl_3). Mass m/z : 354 (M^+). IR

$\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3360, 1620, 1510, 820, 750. ^1H NMR δ : 2.8~3.1 (m, 4H, $-\text{N}(\text{CH}_2)_2$), 3.1~3.4 (m, 4H, $(-\text{CH}_2)_2\text{O}$), 3.6 (broad s, 2H, $-\text{NH}_2$), 6.9~8.2 (m, 12H, aromatic protons).

Preparation of 2,4-dimethylglutaric anhydride 2. The mixture of *cis* and *trans*-isomers was prepared, and *cis*-**2** was isolated according to Wiley.¹³⁾ The more soluble *trans*-**2** was obtained as follows from the mother liquid from which *cis*-**2** was excluded. After hydrolyzing crude *trans*-**2** in boiling water, the diacid was recrystallized from EtOAc three times (mp 140~141°C). Treatment with acetic anhydride at 100°C for 1 hr and distillation gave *trans*-**7**, bp 152~154°C/20 mmHg, ^1H NMR δ : 1.43 (d, $J=7.6$ Hz, 6H, $2 \times \text{CH}_3$), 1.96 (t, $J=6.6$ Hz, 2H, $-\text{CH}_2-$), 2.7~3.1 (m, 2H, $2 \times -\text{CH}(\text{CH}_3)-$). The purity of each isomer was confirmed by GLC (temperature 120°C).

Synthesis of (2*R*,4*S*)-2,4-dimethyl- δ -valerolactone 8. With **1c** (Table I, run 2): *cis*-2,4-Dimethylglutaric anhydride (*cis*-**2**, 0.19 g, 1.3 mmol) was added to a solution of **1c** (0.47 g, 1.3 mmol) in toluene (15 ml) at -20°C . The mixture was allowed to stand at -20°C for 3 days and then treated with an ethereal solution of diazomethane. To a solution of **7b** in dry EtOH (10 ml), LiCl (0.17 g, 3.9 mmol) and NaBH_4 (0.15 g, 3.9 mmol) were added with ice-cooling. The mixture was heated at 50°C for 24 hr. After cooling, 3 N HCl (20 ml) was added and the mixture was extracted with CH_2Cl_2 (30 ml $\times$ 3). The combined extracts were washed with sat. NaCl, dried over anhyd. Na_2SO_4 and evaporated. 2 N Sulfuric acid (20 ml) and dioxane (4 ml) were added to the residue, and the mixture was heated at 80°C for 2 hr. After cooling, the solution was extracted with ether (30 ml $\times$ 5). The combined extracts were washed successively with 3 N HCl three times and sat. NaCl, and then dried over anhyd. Na_2SO_4 . Evaporation gave **8** as an oil (0.16 g, 77%). An analytical sample was obtained with preparative GLC (column temperature, 150°C). $[\alpha]_D^{25} - 37.8^\circ$ ($c=1.3$, CHCl_3) 92% *e.e.*

With **1a** (Table I, run 1): To a solution of **1a** (1.0 g, 3.5 mmol) in benzene (35 ml), a solution of *cis*-**2** (0.65 g, 4.6 mmol) in benzene (15 ml) was added at room temperature. After stirring at room temperature overnight, diazomethane was added. The product was subjected to MPLC (silica gel, 20% EtOAc in hexane) to afford each diastereomer. (2*S*,4*R*)-**7a** (0.24 g, 15.5%), glass; $[\alpha]_D^{25} - 50.0^\circ$ ($c=1.03$, CHCl_3); mass m/z : 440 (M^+); ^1H NMR (100 MHz) δ : 0.82 and 0.96 ($2 \times \text{d}$, $J=7.2$ Hz, 6H, $2 \times \text{CH}_3$), 1.0~1.4, 1.7~2.1 and 2.2~2.5 (m, 4H, $-\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}(\text{CH}_3)-$), 3.48 (s, 3H, OCH_3), 3.8 (broad s, 2H, $-\text{NH}_2$), 6.8~8.0 (m, 12H, aromatic protons), 8.43 and 8.52 ($2 \times \text{s}$, 1H, $-\text{NHCO}-$). (2*R*,4*S*)-**7a** (0.69 g, 44.5%), mp 149~150°C; $[\alpha]_D^{25} - 52.6^\circ$ ($c=1.07$, CHCl_3); mass m/z : 440 (M^+); ^1H NMR (100 MHz) δ : 0.77 and 0.94 ($2 \times \text{d}$, $J=7.2$ Hz, $2 \times \text{CH}_3$), 1.1~1.3 and 1.5~2.4 (m, 4H, $-\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}(\text{CH}_3)-$), 3.4 (broad s, 2H, $-\text{NH}_2$), 3.51 (s, 3H, OCH_3), 6.8~8.1 (m, 12H, aromatic

protons), 8.50 and 8.59 ($2 \times \text{s}$, 1H, $-\text{NHCO}-$).

Acetic anhydride (0.29 g, 2.8 mmol) and triethylamine (0.28 g, 2.8 mmol) were added to a solution of (2*R*,4*S*)-**7a** (0.60 g, 1.4 mmol) in CH_2Cl_2 (5 ml) at 0°C . The mixture was stirred at room temperature overnight. After adding sat. NaHCO_3 (10 ml), the mixture was extracted with CH_2Cl_2 (20 ml $\times$ 3). The combined extracts were washed with sat. NaCl and dried over anhyd. Na_2SO_4 . Evaporation gave the acetylated **7a** (0.63 g). This product was reduced and hydrolyzed according to the previous procedure to afford **8** (0.08 g, 46%), $[\alpha]_D^{25} - 42.4^\circ$.

Synthesis of (R)-mevalonolactone 9. To a solution of 3-hydroxy-3-methylglutaric anhydride (**3**, 0.29 g, 2.0 mmol) in CH_2Cl_2 (30 ml), **1d** (0.79 g, 2.0 mmol) was added at -20°C . The mixture was allowed to stand at -20°C for 7 days. After treating with diazomethane, the amide-ester **7e** was reduced as described in the synthesis of **8** from **7b**. After working up, alkaline hydrolysis was carried out using 10% KOH in MeOH (20 ml) at 60°C for 4 hr. After neutralizing with 2 N H_2SO_4 , MeOH was distilled off under reduced pressure. The aqueous solution was continuously extracted with ether at pH 3.0 for 3 days. The extract was dried over anhyd. Na_2SO_4 and evaporated. The residue was subjected to preparative TLC (silica gel, 33% EtOAc in benzene) to afford **9** (0.11 g, 44%), $[\alpha]_D^{25} - 12.2^\circ$ ($c=6.0$, EtOH). Determination of the *e.e.* of **9** was performed with ^1H NMR (400 MHz) according to Wilson.¹⁸⁾ Peak separation was observed at a proton adjacent to the carbonyl group; **9** (30.4 mg) and Eu(hfc)₃ (45.0 mg) in CDCl_3 (680 mg).

Synthesis of (R)-3-isopropyl- δ -valerolactone 10. To a solution of **1b** (0.5 g, 1.3 mmol) in toluene (10 ml), 3-isopropylglutaric anhydride (**4**, 0.23 g, 1.5 mmol) was added at room temperature. After stirring overnight, diazomethane was added. By the same treatment for the synthesis of **8** from **7b**, the amide-ester **7f** was converted to **10** (0.05 g, 38%), $[\alpha]_D^{25} + 7.1^\circ$ ($c=0.83$, EtOH). The amide-ester **7f** was separated into each diastereomer with MPLC (silica gel, 12% EtOAc in hexane). (3*S*)-**7f**, glass; $[\alpha]_D^{25} - 57.8^\circ$ ($c=0.54$, CHCl_3); mass m/z : 550 (M^+); ^1H NMR (400 MHz) δ : 0.61 ($2 \times \text{d}$, $J=6.8$ Hz, 6H, $2 \times \text{CH}_3$), 1.19~1.29 (m, 1H, $-\text{CH}(\text{CH}_3)_2$), 1.66~1.74, 1.76~1.84 and 2.08~2.13 (m, 5H, $-\text{CH}(\text{CH}_2)_2$), 3.47 (s, 3H, OCH_3), 7.04~8.74 (m, 14H, $2 \times -\text{CONH}-$ and aromatic protons). (3*R*)-**7f**, glass; $[\alpha]_D^{25} - 73.8^\circ$ ($c=1.01$, CHCl_3); mass m/z : 550 (M^+); ^1H NMR (400 MHz) δ : 0.52 and 0.66 ($2 \times \text{d}$, $J=6.8$ Hz, 6H, $2 \times \text{CH}_3$), 1.07~1.15 (m, 1H, $-\text{CH}(\text{CH}_3)_2$), 1.66~1.77 and 1.96~2.12 (m, 5H, $-\text{CH}(\text{CH}_2)_2$), 3.51 (s, 3H, OCH_3), 7.05~8.55 (m, 14H, $2 \times -\text{CONH}-$ and aromatic protons).

Synthesis of (2*R*,3*S*)-2,3-methylene- γ -butyrolactone 11. To a solution of **1b** (1.14 g, 3.0 mmol) in toluene (15 ml), 1,2-cyclopropanedicarboxylic anhydride (**5**, 0.4 g, 3.6 mmol) was added at room temperature. After stirring

overnight, diazomethane was added. By the same treatment as described in the synthesis of **8** from **7b**, the amide-ester **7g** was converted to **11** (0.19 g, 65%). $[\alpha]_D^{25} + 28.0^\circ$ ($c = 6.41$, CHCl_3).

The ring opening reaction of cis-1,2-cyclohexane-dicarboxylic anhydride 6 with 1a. To a solution of **1a** (0.5 g, 1.75 mmol) in benzene (15 ml), **6** (0.27 g, 1.75 mmol) was added at room temperature. Stirring was continued at room temperature for 72 hr and diazomethane was added. Evaporation gave a diastereoisomeric mixture of **7h**, and this was subjected to MPLC (silica gel, 10% EtOAc in hexane). The isomer eluting faster (0.08 g, 10%, glass; $[\alpha]_D^{25} - 30.3^\circ$ ($c = 1.03$, CHCl_3); mass m/z : 452 (M^+); ^1H NMR (100 MHz) δ : 0.8~2.1 (m, 8H, $-(\text{CH}_2)_4-$), 2.3~2.6 and 2.6~2.9 (m, 2H, $-\text{COCHCHCO}-$), 3.5 (broad s, 2H, $-\text{NH}_2$), 3.52 (s, 3H, OCH_3), 6.8~8.0 (m, 12H, aromatic protons), 8.52 and 8.61 ($2 \times$ s, 1H, $-\text{NHCO}-$). The isomer eluting slower (0.18 g, 22%), mp $165 \sim 166^\circ\text{C}$; $[\alpha]_D^{25} - 28.7^\circ$ ($c = 1.35$, CHCl_3); mass m/z : 452 (M^+); ^1H NMR (100 MHz) δ : 0.8~2.1 (m, 8H, $-(\text{CH}_2)_4-$), 2.4~2.7 (m, 2H, $-\text{COCHCHCO}-$), 3.5 (broad s, 2H, $-\text{NH}_2$), 3.48 (s, 3H, OCH_3), 6.8~8.0 (m, 12H, aromatic protons), 8.52 and 8.62 ($2 \times$ s, 1H, $-\text{NHCO}-$).

Synthesis of (2R,4R)-dimethyl- δ -valerolactone 12 through kinetic resolution. To a solution of **1c** (0.53 g, 1.5 mmol) in toluene (25 ml), *trans*-**2** (1.1 g, 7.5 mmol) was added at -20°C . After stirring at -20°C for 2 days, diazomethane was added. After expelling the excess diazomethane, the solution was treated with propylamine (0.47 g, 7.9 mmol) at room temperature for 1 hr. The mixture was washed with sat. NaHCO_3 three times and dried over anhyd. Na_2SO_4 . Evaporation gave the amide-ester **7b**, which was reduced and hydrolyzed as described for the *cis* counterpart of **7b**. Distillation gave **12** (0.09 g, 47%), bp $135^\circ\text{C}/15\text{ mmHg}$. $[\alpha]_D^{20} - 60.1^\circ$ ($c = 2.13$, CHCl_3). The ^1H NMR spectrum (400 MHz) is depicted in Fig. 1.

The *trans* lactone **12** was also yielded using **1d** according to this same procedure in a yield of 41%. $[\alpha]_D^{20} - 53.4^\circ$ ($c = 1.9$, CHCl_3).

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