OPTICAL RESOLUTION OF FRAGRANT LACTONES

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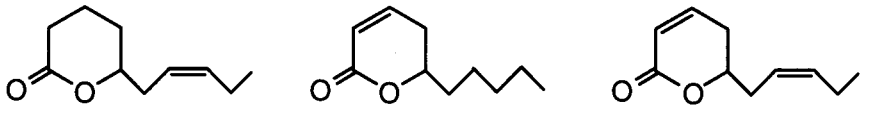
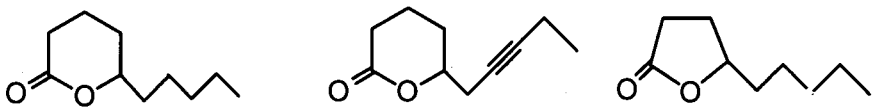
Abstract–Optical resolution of six chiral fragrant lactones (δ-jasmine lactone, massoia lactone, tuberolactone, pentynyllactone, δ-decalactone, and γ-nonalactone) was investigated by means of either the diastereomeric salt formation method or the diastereomeric amide formation method. Using these procedures, we obtained each enantiomer from five of the six lactones, except for massoia lactone. All five lactones were obtained in a good yield and with high optical purity. Sensoric characteristics on both enantiomers and racemic modification of four lactones are given.

Saturated and unsaturated aliphatic δ-lactones, which occur naturally in food and essential oils, play an important role as flavoring agents. Many flavor and fragrance compounds are chiral, and enantiomers differ primarily in their fragrance character. In most cases, the odor quality of optically pure substances is superior to that of racemic material. Considerable effort has been devoted to the development of economical methods for the industrial synthesis of pure enantiomers. However, to date only a small proportion of all utilized chiral flavor and fragrance chemicals has been commercially manufactured by separation of racemate or by enantioselective total synthesis.[1,2] We investigated the optical resolution of six synthetic fragrant lactones, including δ-jasmine lactone (**1**), massoia lactone (**2**), tuberolactone (**3**), δ-decalactone (**4**), pentynyllactone (**5**), and γ-nonalactone (**6**). All of them (**1**–**6**) have a chiral center at the joint of the alkyl chain on their lactone rings. We may expect that these lactones can be separated to each enantiomer by diastereomeric salt formation method or diastereomeric amide formation

method. This simplifies the practical application of these lactones for the industrial production of optically active compounds. Moreover, investigating the structure–odor correlations of naturally occurring chiral flavor and fragrance components is of fundamental importance.



Jasmine lactone **1** | Massoia lactone **2** | Tuberolactone **3**



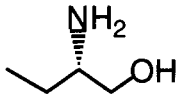
δ-Decalactone **4** | Pentynyllactone **5** | γ-Nonalactone **6**

Chart 1

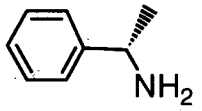
In the preceding papers, structure and properties of **6**,[1] synthesis of both enantiomers of **1** and **5** from chiral synthons,[2] an enantiospecific route to (*R*)-**2** from (*R*)-epichlorohydrin,[3] and chirospecific analysis and fragrance and flavor research of **1**, **3**, **4**, and **6** by chiral inclusion gas chromatography[4] were reported. However, no optical resolution studies of these lactones *via* the diastereomeric salt or amide formation and successive fractional crystallization method have been reported due to the fact that diastereomers of aliphatic lactones do not readily crystallize. A number of resolving agents were applied to form diastereomeric crystals from these lactones, and various solvents for fractional crystallization were examined to obtain an efficient resolution procedure. We recently reported establishment of an efficient resolution procedure for **2** using 1-aminotetralin as a resolving agent.[5] In this report, we describe the optical resolution of **1**, **3**, **4**, **5**, and **6** in detail.

1. OPTICAL RESOLUTION OF JASMINE LACTONE (1) *VIA* THE FORMATION OF DIASTEREOMERIC SALT

In order to apply the diastereomeric salt formation method, stable (±)-**1** was converted to (±)-5-hydroxy-7-decenoic acid (**7**) sodium salt using an aq. NaOH solution. Salt exchange was completed by treating the sodium salt with an equimolecular amount of aq. solution of an optically active amine hydrogen chloride at pH 7. After being left to stand overnight, crude diastereomeric salt was precipitated



(*S*)-(+)-2-Amino-1-butanol



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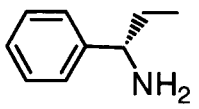
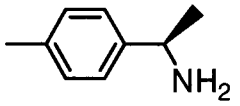
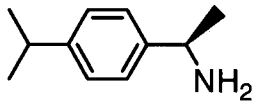
(*S*)-(-)-α-Methylbenzylamine



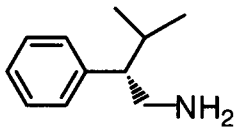
(*S*)-(-)-α-Ethylbenzylamine



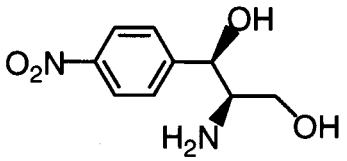
(*R*)-(+)-*p*-Tolylethylamine



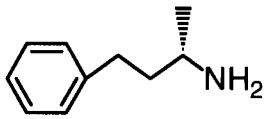
(*R*)-(+)-1-(4-Isopropylphenyl)ethylamine



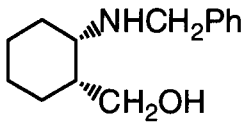
(*S*)-(-)-3-Methyl-2-phenyl-1-butylamine



(*1R, 2R*)-(-)-*threo*-2-Amino-1-(*p*-nitrophenyl)-1,3-propanediol



(*S*)-(+)-4-Phenyl-2-butylamine



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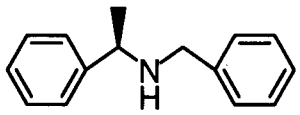
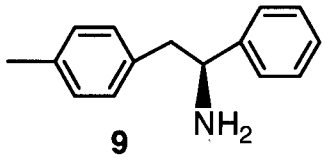
(*1R, 2S*)-(+)-(*cis*-2-Benzylaminocyclohexyl)methanol



(*R*)-(+)-*N*-Benzyl-α-methylbenzylamine



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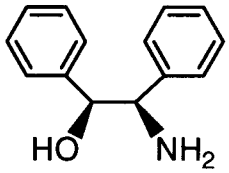
(*S*)-(+)-1-Phenyl-2-(*p*-tolyl)ethylamine



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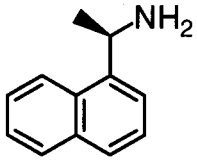
(*1S, 2R*)-(+)-*erythro*-2-Amino-1,2-diphenylethanol



19

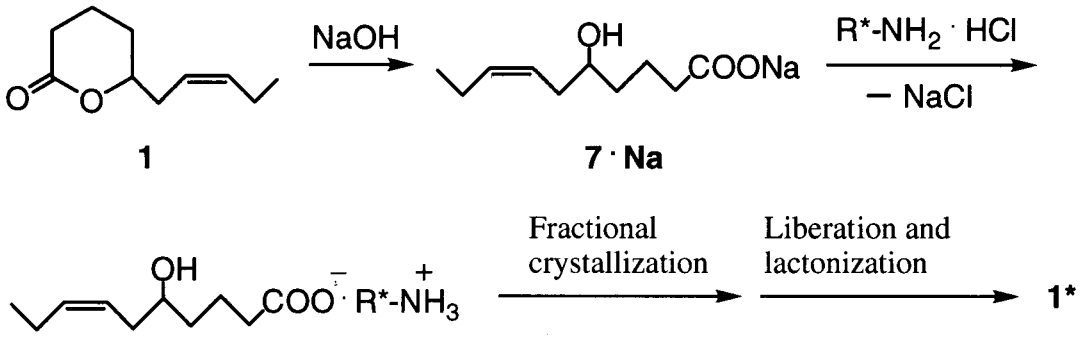
(*R*)-(+)-1-(1-Naphthalenyl)ethylamine

Brucine **Quinine**

Chart 2 Basic resolving agents examined.

and filtered off. When no precipitate appeared, the solvent was exchanged from H_2O to 99% ethanol to remove sodium chloride. The diastereomeric salt obtained after sodium chloride removal was subjected to fractional crystallization. Then the salt was treated with aq. NaOH solution to liberate the resolving

agent which was extracted using ether. The remaining sodium carboxylate was transformed to **7** *via* treatment with aq. HCl, followed by lactonization with *p*-toluenesulfonic acid in benzene to yield optically active **1** (Scheme 1).



Scheme 1

Table 1. Results of trial resolution of **1** by various chiral amines

Resolving agent	Yield[a](%)	Optical purity[b](% ee)	Efficiency[c]
8	79.8	70.0	55.9
9	71.1	0.0	0
10	49.9	3.0	1.5

a) Based on half the amount of racemate. b) Determined by HPLC analysis. c) Yield (%) × optical purity (%ee) ÷ 100.

Table 2. Optimization of recrystallization solvent using (*1S, 2R*)-(+)-**8** as a resolving agent

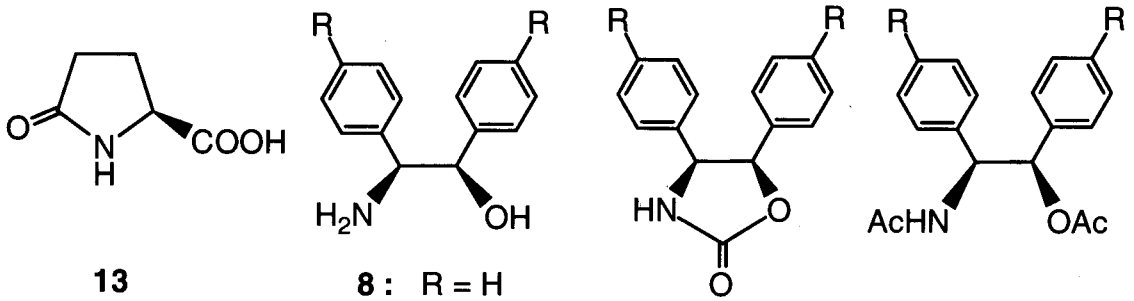
Recrystallization solvent	Yield of diastereomeric salt[a](%)	mp[b](℃)	Optical purity[c](% ee)	Efficiency[d]
Ethyl acetate	133	109 - 123	15.3	20.3
H_2O	79.8	134 - 136	70.0	55.9
2-Propanol	75.6	128 - 131	46.2	34.9
Ethanol : H_2O (1 : 1)	66.6	128 - 135	46.5	31.0
Methanol : H_2O (1 : 4)	95.6	125 - 134	25.9	24.8
Acetone : H_2O (1 : 4)	96.2	120 - 131	16.0	15.4

a) Based on half the amount of racemate. b) Mp of diastereomeric salts. c) Determined by specific rotation of **1**. d) Yield (%) × optical purity (% ee) ÷ 100.

Following the above procedure, fifteen chiral amines (Chart 2) were used as basic resolving agents. Among the various agents, only three formed crystalline diastereomeric salts (Table 1). As shown in Table 1, *erythro*-2-amino-1,2-diphenylethanol (**8**) was found to be the most effective resolving agent due to the fact that it showed the greatest resolving efficiency. Using (*1S, 2R*)-(+)-**8** as a resolving agent, we optimized the resolving conditions to obtain enantiomerically enriched (*R*)-**1**. Various solvents were compared for use in fractional crystallization (Table 2). The result showed that water was the most effective solvent.

2. SYNTHESIS AND RESOLUTION OF *p*-SUBSTITUTED 2-AMINO-1,2-DIPHENYLETHANOLS (11, 12)

As compound (**8**) is an efficient resolving agent for jasmine lactone (**1**), we performed synthesis and resolution of *p*-substituted *erythro*-2-amino-1,2-diphenylethanols (**11** and **12**), both of which are homologs of **8**. These amines (**8**, **11**, and **12**) were investigated in terms of their application as resolving agents for fragrant δ-lactones (**1**–**5**) in order to compare the resolving efficiency of **11** and **12** with that of **8** (Chart 3).



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8: R = H
11: R = CH_3
12: R = OCH_3

14: R = H
15: R = CH_3

16: R = OCH_3

Chart 3

Racemic amines (**8**, **11**, and **12**) were synthesized in a high yield from their corresponding benzoins as starting materials. All three were converted to their corresponding oximes with hydroxylamine, followed by catalytic hydrogenation using 5% palladium-carbon catalyst.[6] All *erythro*-2-amino-1,2-diphenylethanols (**8**, **11**, and **12**) obtained were optically resolved efficiently by the diastereomeric salt formation method using (*S*)-(-)-pyroglutamic acid (**13**) as a resolving agent (Table 3). Optical purities of **8** and **11** were determined by chiral HPLC analysis (Daicel CHIRALCEL OJ and OD-H) using their

oxazolidinone derivatives (**14** and **15**) obtained using triphosgene in toluene. The optical purity of **12** was determined by CHIRALPAK AD using its diacetylated derivative (**16**) obtained using acetic anhydride in THF (Chart 3).

Next, all three amines (**8**, **11**,and **12**) were used to resolve δ-lactones (**1–5**) following the same procedure as that in Scheme 1. The results are summarized in Table 4.

Table 3. Optical resolution of **8**, **11**, and **12** by (*S*)-(-)-pyroglutamic acid (**13**)

Aminoalcohol	Solvent	Yield[a](%)	Optical purity[b](% ee)	Efficiency[c]
8	H_2O	85.8	>99	85.8
11	MeOH	57.3	>99	57.3
12	H_2O	86.3	>99	86.3

a) Based on half the amount of racemate. b) Determined by HPLC analysis. c) Yield (%) × optical purity (% ee) ÷ 100.

Table 4. Efficiency of optical resolution of δ-lactones (**1–5**) by **8**, **11**, and **12**

Resolving agent \ δ-Lactone	**1**	**2**	**3**	**4**	**5**
8	49.6	13.7	35.7	1.4	55.3
11	21.5	11.9	33.9	22.5	35.6
12	2.9	10.2	24.5	2.4	15.8

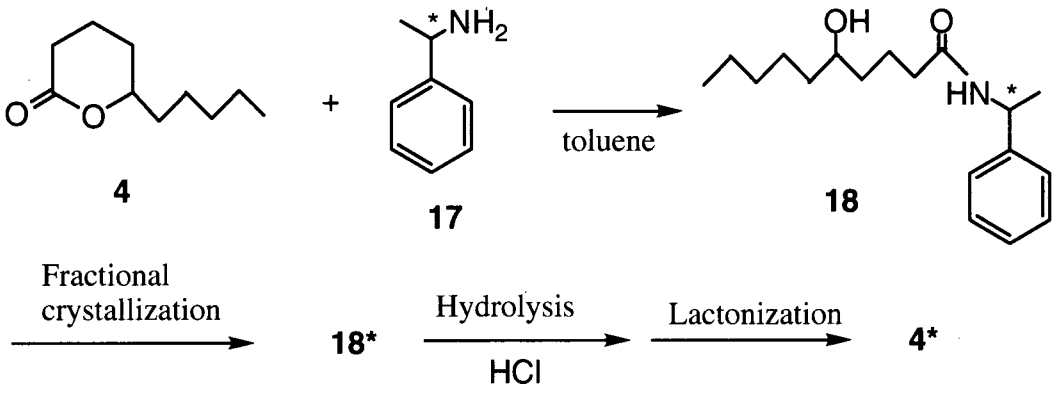
Based on the above data, we concluded that compound (**8**) is the best resolving agent for **1**, **3**, and **5** due to the fact that it showed the greatest resolving efficiency. Likewise, compound (**11**) was found to be the best for **4**. Compound (**12**) was determined to be the least efficient of any of the amines (**8**, **11**). We also found that none of resolving agents (**8**, **11**,and **12**) are effective for massoia lactone (**2**). Thus, the introduction of *p*-methyl or *p*-methoxy group on the benzene ring was shown to influence resolving efficiency.

3. OPTICAL RESOLUTION OF δ-DECALACTONE (4) *VIA* THE FORMATION OF DIASTEREOMERIC AMIDE

Racemic δ-decalactone (tetrahydro-6-pentyl-2*H*-pyran-2-one, **4**) is one of a number of synthetic

fragrance materials. It is now marketed as a flavoring agent in butter and cream. Initially, we attempted optical resolution *via* the diastereomeric salt formation method using six basic amines. Two salts were crystallized, but both showed low resolving efficiency. As shown in Table 4, **4** is optically resolved *via* the diastereomeric salt formation method using **11** as a resolving agent. However, the resolving efficiency is too low to make application on an industrial scale economically feasible. Next, we investigated optical resolution *via* the diastereomeric amide formation method. In this method, it is important to note that, (i) diastereomeric amide formed can be crystallized, (ii) fractional crystallization leads to the separation of diastereomerically pure amide, and (iii) no racemization occurs on hydrolysis of the pure amide. We have found that the amide formation method using α-methylbenzylamine (**17**) toward **4** is more effective than the salt formation method applying various amines to **4**. Agent (**17**) is one of the most practical basic resolving agents.

Reaction of racemic δ-decalactone (**4**) using an equimolar amount of optically active **17** in anhydrous benzene or toluene at an elevated temperature led to diastereomeric amides (**18**). Using four cycles of fractional crystallization of the amides with toluene, diastereomerically pure amide was obtained in a 50.4% yield, 98.2% de. Hydrolysis of the amide (6M HCl in 95% EtOH) and successive lactonization (*p*-TsOH, benzene) followed by distillation produced optically pure **4** in a 47.8% yield, 98.1% ee, indicating that no racemization occurred during the hydrolysis stage (Scheme 2) (Table 5).



Scheme 2

Table 5. Results of optical resolution of **4** *via* diastereomeric amide formation with **17**

Diastereomeric amide or enantiomer	Yield[a](%)	$[\alpha]_D$ (°)	mp(℃)	Optical purity[d]
(+)-**4** (–)-**17**	50.4	–77.9[b]	108–111	98.2 de
(–)-**4** (+)-**17**	17.0	+76.6[b]	106–111	96.8 de
(*R*)-(+)-**4**	47.8	+56.7[c]	–	98.1 ee
(*S*)-(–)-**4**	10.0	–55.5[c]	–	97.9 ee

a) Based on half the amount of racemate. b) c 1.00, MeOH. c) c 1.7, THF. d)Determined by HPLC analysis.

γ-Nonalactone [dihydro-5-pentyl-2(3*H*)-franone, **6**] is present in coconut oil, butter, tropical fruits, and other substance in nature, and at present **6** is produced as racemic modification.[1] In a similar manner as with **4**, we succeeded in optical resolution of **6** *via* an amide formation method using 1-(1-naphthalenyl)ethylamine (**19**) as a resolving agent (Table 6).

Table 6. Results of optical resolution of **6** via diastereomeric amide formation with **19**

Diastereomeric amide or enantiomer	Yield[a](%)	$[\alpha]_D$[b] (°)	mp(℃)	Optical purity
(+)-**6** (+)-**19**	20.1	+22.9	135–139	>99.9 de[c]
(–)-**6** (–)-**19**	30.2	–25.8	135–139	97.8 de[c]
(*R*)-(+)-**6**	14.4	+49.2	–	94.8 ee[d]
(*S*)-(–)-**6**	20.5	–48.1	–	>99.9 ee[e]

a) Based on half the amount of racemate. b) c 1.00, MeOH. c) Determined by HPLC (CHIRALPAK AD). d) Based on the literature value; $[\alpha]_D$ + 51.8° (c 1.00, MeOH)[1]. e) Determined by HPLC (CHIRALCEL OB-H).

4. FRAGRANCE CHARACTER

A sensory test was carried out on both enantiomers and racemic modification of **1**–**4**. The resulting sensory profiles are summarized in Table 7.

Table 7. Fragrance character of δ-lactones (**1**–**4**)[a)]

δ-Lactone	Racemate	(*R*)	(*S*)
1	Fatty–creamy–nutty–milky–flowery	Nutty–milky, jasmin-like	Fatty–creamy, tuberoseflower-like
2[5]	Fatty–sweet–nutty, coconut-like	Fresh–fatty–sweet, coconut-like, coumarin-like	Oily–fatty–sweet,
3	Nutty, fatty, tuberoseflower-like	Fatty, tuberoseflower-like	Oily–fatty, fruity
4	Creamy, nutty	Fruity–milky	Fruity-sweet

a) Tested by smelling strips; solution (1%, 95 v/v % ethanol).

EXPERIMENTAL

(*S*)-(+)-2-Amino-1-butanol, (*1R, 2R*)-(-)-*threo*-2-amino-1-(*p*-nitrophenyl)-1,3-propanediol, (*S*)-(+)-1-phenyl-2-(*p*-tolyl)ethylamine, brucine, and quinine were purchased from Tokyo Chemical Industry Co., Ltd.. (*S*)-(-)-α-Methylbenzylamine, (*R*)-(+)-*p*-tolylethylamine, (*R*)-(+)-*N*-benzyl-α-methylbenzylamine, (*1S, 2R*)-(+)-*erythro*-2-amino-1,2-diphenylethanol, (*R*)-(+)-1-(1-naphthalenyl)ethyl amine were gifted from Yamakawa Chemical Industry Co., Ltd.. (*S*)-(-)-α-Ethylbenzylamine,[7] (*R*)-(+)-1-(4-isopropylphenyl)ethylamine,[8] and (*1R, 2S*)-(+)-(*cis*-2-benzylaminocyclohexyl)methanol[9] were synthesized as previously reported. (*S*)-(-)-3-Methyl-2-phenyl-1-butylamine and (*S*)-(+)-4-phenyl-2-butylamine were obtained from the optical resolution of each racemate using optically active mandelic acid and 2-(2,5-dimethylphenyl)propionic acid as resolving agents, respectively. Ir spectra were recorded on a PERKIN-ELMER FT-1640 spectrometer. ^{1}H NMR spectra were measured on a VARIAN GEMINI 2000 spectrometer. All melting point (mp) values were uncorrected. Specific rotations were measured with a JASCO DIP-370 polarimeter. Optical purities were determined by HPLC using INERTSIL 5SIL (4.6 mm x 250 mm), WAKOSIL 5SIL (4.6 mm x 250 mm), and a set of JASCO LC 900 series equipped with chiral columns (Daicel Chem. Ind., Ltd., 4.6 mm x 250 mm).

OPTICAL RESOLUTION OF δ-JASMINE LACTONE (**1**)

To open the lactone ring, a solution of (±)-**1** (2.524 g, 15 mmol) in 1M NaOH (22.5 mL) was stirred for 20 min at 70℃, and then H_2O (25.0 mL) and aq. 1M HCl were added until pH 7 at rt. A solution of (*1S, 2R*)-(+)-**8** (2.879 g, 13.9 mmol) dissolved in 1 M HCl (15.0 mL) and H_2O (45 mL) was added to

the mixture. After heating at 100℃, the mixture was allowed to stand overnight at rt. The precipitates that formed were filtered off and a crude diastereomeric salt **7** · (+)-**8** (3.836 g, 9.60 mmol) was obtained. Three cycles of recrystallization of the salt from H_2O gave diastereomerically pure salt (1.305 g, mp 141–142℃, $[\alpha]_D$ + 67.5° (c 1.00, MeOH)) in a 43.6% yield. The salt was then decomposed using 1 M NaOH (6.5 ml) and the resolving agent (+)-**8** was extracted using ether. 1 M HCl (7.0 mL) was added to the remaining solution and extracted using ether. After evaporation of the solvent, *p*-toluenesulfonic acid (23 mg) in benzene (2.0 mL) was added and the solution was heated for 1 h. The reaction mixture was then quenched by adding saturated aq. NaCl and 5 wt% $NaHCO_3$, and concentrated. Distillation of the residue under reduced pressure (105℃/2 torr) gave 371 mg (2.205 mmol, in a 29.4% total yield based on half the amount of used (±)-**1**) of 98.7% ee (*R*)- (-)-**1** ($[\alpha]_D$ – 17.3° (c 0.38, $CHCl_3$)). The mother liquor from the original crystallization was concentrated under reduced pressure to yield easily soluble diastereomeric salt **7** · (+)-**8** (3.201 g, 8.01 mmol), followed by a similar treatment with 1 M NaOH (12.8 mL), the removal of (+)-**8** by extraction, and neutralization of the residue with 1 M HCl. To the residue was added a solution of (*1R, 2S*)-(-)-**8** (1.642 g, 7.70 mmol) dissolved in 1 M HCl (8.6 mL) and H_2O (34 mL). The mixture was refluxed at pH 7 and allowed to cool slowly at rt to yield crude salt **7** · (-)-**8** (1.861 g, 4.66 mmol). Only one cycle of recrystallization of the salt with H_2O was used to produce diastereomerically pure salt (1.213 g, 3.04 mmol, mp 136 –141℃, $[\alpha]_D$ – 66.9° (c 1.00, MeOH)) in a 40.5% yield, from which 344 mg (27.3% yield) of 96.5% ee (*S*)-(+)-**1** (98℃/1 torr, $[\alpha]_D$ + 17.6° (c 0.38, $CHCl_3$)) was obtained. The optical purities of (*R*)- (–)-**1** and (*S*)-(+)-**1** were determined based on the amide derivatives obtained by treatment with optically pure 1-(1-naphthalenyl)ethylamine (**19**) by HPLC analysis [column, INERTSIL 5SIL; eluent, ethyl acetate/*n*-hexane (1/1); flow rate, 1.0 mL/min; detection, 254 nm].

SYNTHESIS OF *erythro*-2-AMINO-1,2-DIANISYLETHANOL (12)

A solution of hydroxylamine hydrochloride (0.695 g, 10.0 mmol) in 2M NaOH (4.0 mL) was added to a solution of 4,4'-dimethoxybenzoin (1.36 g, 5.00 mmol) in 95% ethanol (15 mL) and the mixture was refluxed for 3 h. The solution was concentrated under reduced pressure and extracted with ether. The ethereal extract was washed with 1 M HCl and saturated NaCl, and dried using Na_2SO_4. Concentration of the solution gave 4,4'-dimethoxybenzoin α-oxime (1.43 g) in a 99.7% yield.

Next, 4,4'-dimethoxybenzoin α-oxime (2.87 g, 10.0 mmol) was placed in a flask equipped with a condenser and dissolved in acetic acid (20.0 mL). A 5% palladium-charcoal catalyst (0.300 g) was

added to the flask and the suspension was stirred for 60 h at rt under a hydrogen atmosphere. After the reaction was complete, the catalyst was filtered off through a celite and washed with methanol. The filtrate and the washings were combined and 1 M HCl (10 mL) was added. The mixture was concentrated *in vacuo* to remove acetic acid. Water (100 mL) was added to the residue, which was basified with concd aq. ammonia, and stood overnight at rt to give precipitates. The precipitates were collected by filtration and recrystallized from ethanol to give **12** (1.99 g, 7.30 mmol, mp 144–146 ℃) in a 73.0% yield.

IR(KBr)cm^{-1} 3335, 3270, 3096, 1611, 1518, 1256, 1028; ^1H NMR 6.80-7.36 (8H, m, aromatic-H), 4.63 (1H, d, CH(OH), j = 6.6 Hz), 4.06 (1H, d, $CH(NH_2)$, J = 6.6 Hz), 3.80 (6H, s, OCH_3).

OPTICAL RESOLUTION OF (±)-12 WITH (*S*)-(–)-PYROGLUTAMIC ACID (13) BY FRACTIONAL CRYSTALLIZATION

A clear solution of (±)-**12** (2.73 g, 10.0 mmol) and (*S*)-(–)-**13** (1.29 g, 10.0 mmol) in H_2O (20 mL) at an elevated temperature was allowed to cool slowly until it reached rt and left to stand overnight. The white precipitates that formed were collected by filtration to yield 1.73 g (4.31 mmol, 86.3%) of (–)-**12** · (–)-**13** salt: mp 189–193 ℃, $[\alpha]_D^{23}$ – 95.2° (c 0.5, MeOH). Decomposition of the salt (1.684 g, 4.19 mmol) was carried out using 2 M HCl (3 mL) and water (120 mL) by heating and 3 M NaOH (3 mL) was added yielding 1.00 g (3.67 mmol) of (–)-**12**: mp 151–154 ℃, $[\alpha]_D^{24}$ – 10.8° (c 1, MeOH). The optical purity of (–)-**12** was determined as 2-acetoamido-1,2-dianisylethyl acetate (**16**) by HPLC analysis [column, CHIRALPAK AD; eluent, 20% (v/v) 2-PrOH in *n*-hexane; flow rate, 0.5 mL/min; detection, 254 nm].

OPTICAL RESOLUTION OF δ-DECALACTONE (4).

Racemic δ-decalactone (**4**) (3.40g, 20 mmol) and (*S*)-(–)-**17** (2.43 g, 20.0 mmol) were dissolved in anhydrous toluene (10 mL) and stirred for 3 h at 95 ℃. After adding toluene (30 mL) to the mixture, the mixture was heated again and cooled. When the temperature of the reaction mixture reached 50℃, a seed crystal of optically pure amide (**18**), which was prepared in advance, was inoculated in the mixture and allowed to stand overnight at rt. The precipitate that formed was filtered off to yield the crude diastereomeric amide (**18**) (2.16 g, 9.9 mmol). Four times recrystallization of the amide from toluene yield diastereomerically pure amide (–)-**18** [1.47 g, 5.04 mmol, mp 108–111℃, $[\alpha]_D$ – 77.9° (c 1.00, MeOH), 98.2% de]. Diastereomeric excess of the amide was determined by HPLC analysis (WAKOSIL 5SIL). The amide was hydrolyzed using 6 M HCl (3 mL) in 95% ethanol (15 mL) at 90℃

for 5 h to yield 5-hydroxydecanoic acid (0.90 g, 4.8 mmol). The acid was successively refluxed with *p*-toluenesulfonic acid in benzene, followed by distillation gave 98.1% ee of (*R*)-(+)-**4** [0.71 g, 4.2 mmol, $[\alpha]_D$ + 56.7°(c 1.79, THF)] in a 41.9% yield (total yield based on half the amount of racemic **4** used). (–)-Rich-**4** amide (**18**) recovered from the mother liquor of the original crystallization was similarly hydrolyzed using 6 M HCl to yield (–)-rich-**4** (1.62 g, 9.5 mmol), which was used in the next resolution using (*R*)-(+)-**17**. Four times recrystallization of the crude amide gave diastereomerically pure amide (+)-**18** (mp 106 –111℃, $[\alpha]_D$ + 76.6°(c 1.00, MeOH)) in a 17.0% yield, from which 97.9 % ee (*S*)-(–)-**4** ($[\alpha]_D$ – 55.5° (c 1.72, THF)) was obtained. Optical purities of (*R*)-(+)-**4** and (*S*)-(–)-**4** were determined directly by HPLC analysis [column, CHIRALCEL OB-H (250 x 4.6 mm ID); eluent, 4% (v/v) 2-PrOH in *n*-hexane; flow rate, 0.5 ml/min; detection, 220 nm].

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