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Studies on Agents with Vasodilator and β-Blocking Activities. V.[1) Synthesis and Pharmacological Activity of the Optical Isomers of TZC-5665

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Synthesis of the four optical isomers of TZC-5665 (1), a candidate for the treatment of congestive heart failure, was achieved by the reaction of chiral diaminopyridazinone (2) with chiral glycidyl ether (3). The hypotensive and β-blocking activities of 1 and its optical isomers were examined when given intravenously into anesthetized rats. Furthermore these compounds were evaluated for inhibitory activity on cAMP phosphodiesterase III. Among the four optical isomers, R_A,S_B-one (1c) possessed the essential activities of TZC-5665 (1).

Key words chiral pyridazinone; enantioselective synthesis; asymmetric hydrogenation; hypotensive activity; β-blocking activity; phosphodiesterase III-inhibitory activity

In our previous study to develop an agent with vasodilator and β-blocking activities,[1) the phenoxypropanolamine derivative (**1**, TZC-5665) having a pyridazinone moiety on the *N*-alkyl group showed positive inotropic activity based upon the selective inhibition of cAMP phosphodiesterase (PDE) III and was considered to be a candidate for the treatment of congestive heart failure (CHF).[2) Compound **1** has two asymmetric carbons and thus four optical isomers. Each isomer was synthesized by reacting chiral diaminopyridazinone (**2**) with chiral glycidyl ether (**3**) and the pharmacological profile of the products was examined (Chart 1).

Chemistry

Preparation of Chiral Diaminopyridazinone (2) A chiral anilino-pyridazinone (**8**) was prepared for the synthesis of the chiral diaminopyridazinone (**2**). There are several reports on the synthesis of chiral **8**, for example, by racemate resolution on a chiral HPLC column,[3) fractional recrystallization of the tartaric acid salt[4) or stereoselective synthesis from (+)-2-chloropropionic acid.[5) However, these methods cannot readily be scaled up. Thus, another synthesis of chiral **8** *via* 3-aroylbutenoic acid (**4**) was developed by asymmetric hydrogenation using chiral ruthenium diacetate 2,2′-diphenylphosphinobinaphthyl complex (BINAP-Ru) (**5**), as shown in Chart 2.[6)

It was reported that chiral BINAP-Ru (**5**) was an effective catalyst for asymmetric hydrogenation of α,β- or β,γ-unsaturated carboxylic acids having various alkyl, aryl or alkyl groups substituted with an oxygen functionalized group such as a hydroxy or ester group to give the corresponding saturated products quantitatively with high enantiomeric excess (ee).[6b) This method was applied to the unsaturated carboxylic acid (**4**) possessing an acet-

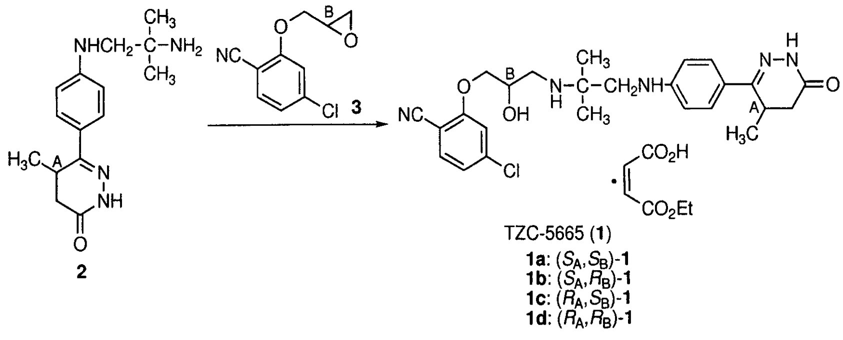

Chart 1

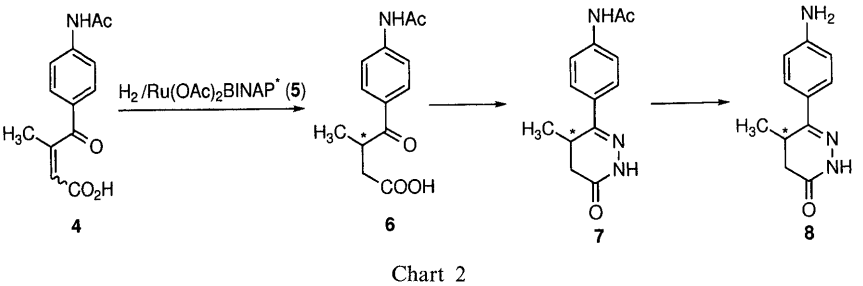

Chart 2

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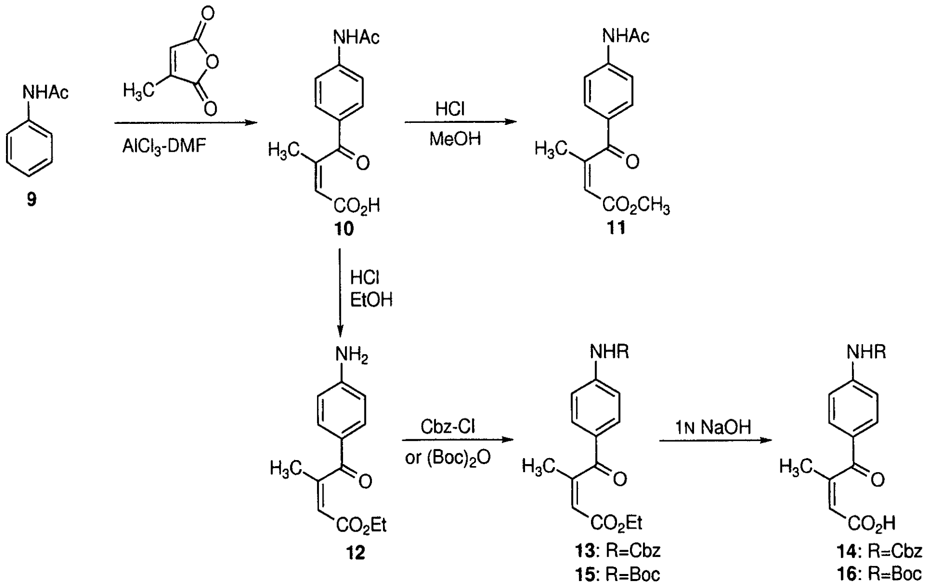


Chart 3

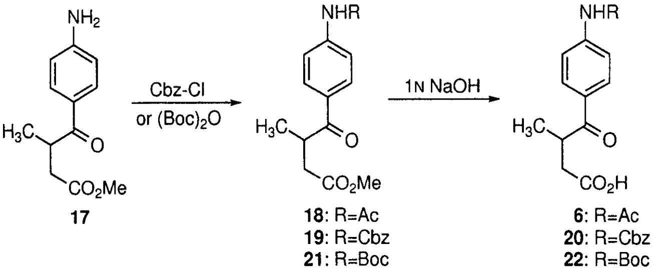


Chart 4

amidobenzoyl group at the β-position in the expectation of efficiently reaching the chiral anilino-pyridazinone (**8**). Thus 3-(4-acetamidobenzoyl)butenoic acids (**10**, **28** and **33**) were prepared as follows.

Synthesis of 3-Aroylbutenoic Acid Derivatives: The Friedel-Crafts acylation of acetanilide (**9**) with citraconic anhydride according to the method of Thyes *et al.*[7] gave 3-(4-acetamidobenzoyl)crotonic acid (**10**)[8] (Chart 3). The structure of the product was confirmed by the NMR spectrum, which showed a doublet methyl proton signal at δ 1.94 (J=1.5 Hz) and a quartet olefinic one at δ 5.94 (J=1.5 Hz). Esterification of **10** with methanolic hydrogen chloride under ice-cooling afforded the ester (**11**), while treatment of **10** at room temperature resulted in concomitant removal of the N-acetyl group to afford the anilino-ester (**12**) as a sole product. Compound **12** was converted to the urethanes (**13** or **15**) with benzyl chloroformate or di-*tert*-butyl dicarbonate and subsequent hydrolysis of the ester group afforded the corresponding 3-aroylcrotonic acids (**14** or **16**). In the same way, a variety of 3-aroylbutyric acid derivatives (**6**, **18**—**22**) were prepared from the ester (**17**)[9] as standard samples for HPLC and TLC (Chart 4).

McEvoy and Allen reported a preparation of several 3-aroylisocrotonic acids by condensation of an appropriate propiophenone with glyoxylic acid.[10] By using this method with the modification of employing a phase-transfer catalyst, the α-hydroxy acid (**24**) was derived from 4-acetamidopropiophenone (**23**).[11] Then **24** was transformed to 3-aroylisocrotonic acid (**28**) *via* the following reaction sequences (Chart 5). Treatment of **24** with methanolic hydrogen chloride gave the corresponding α-hydroxy ester (**25**), whose NMR spectrum showed a pair of doublet methyl proton signals at δ 1.28 and 1.36 in a ratio of 2 : 1, indicating the presence of the two diastereomers. Without separation, O-mesylation of **25** followed by elimination of methanesulfonic acid with excess 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) afforded the α,β-unsaturated ester (**27**) with the desired E-configuration as a single product. The stereochemistry of the double bond was confirmed by comparison of the NMR spectra of the E-isomer (**27**) and Z-isomer (**11**). The former showed a doublet methyl proton signal at δ 2.40 and a quartet olefinic proton signal at δ 6.11, and the latter at δ 2.12 and 6.02, respectively. Then, the ester (**27**) was hydrolyzed to the 3-aroylisocrotonic acid (**28**).

3-(4-Acetamidobenzoyl)-3-butenoic acid (**33**) was prepared by two different methods as shown in Chart 6. Firstly, 3-aroylpropionic acid (**29**)[12] was converted to methyl 3-(4-acetamidobenzoyl)-3-butenoate (**32**) in 3 steps according to the method of Mitchell *et al.*[13] Hydrolysis of **32** gave **33**. The second route involved the β-aroyl-γ-butyrolactone (**35**).[14] Reaction of **29** with formaldehyde in aqueous sodium hydroxide,[15] followed by treatment of the resulting hydroxymethyl derivative (**34**) with hydrochloric acid gave the lactone (**35**). Ring opening of **35** with equimolar sodium methoxide gave the desired **33**. The structure of **33** was confirmed on the basis of the NMR spectrum showing a singlet α-methylene proton signal at δ 3.51 and two singlet γ-olefinic ones at δ 5.71 and 5.99.

Asymmetric Hydrogenation of 3-Aroylbutenoic Acid Derivatives Using Chiral BINAP-Ru (**5**): Homogeneous asymmetric hydrogenation of 3-aroylbutenoic acid (**4**) to the chiral butyric acid (**6**) using 0.25 mol% of chiral BINAP-Ru (**5**) was carried out at room temperature under 60—130 atm of hydrogen according to a reported method.[6] The corresponding methyl ester (**18**) of **6** showed two peaks on HPLC using a chiral stationary phase at the

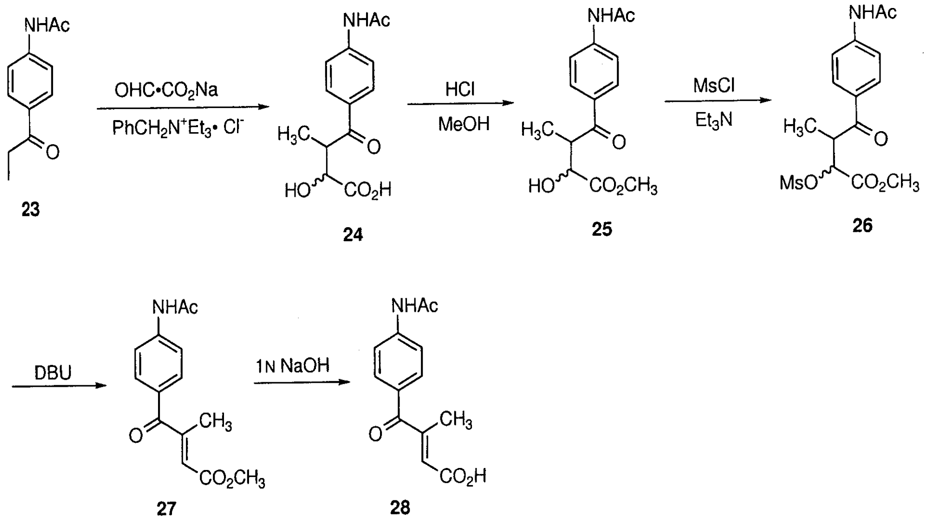


Chart 5

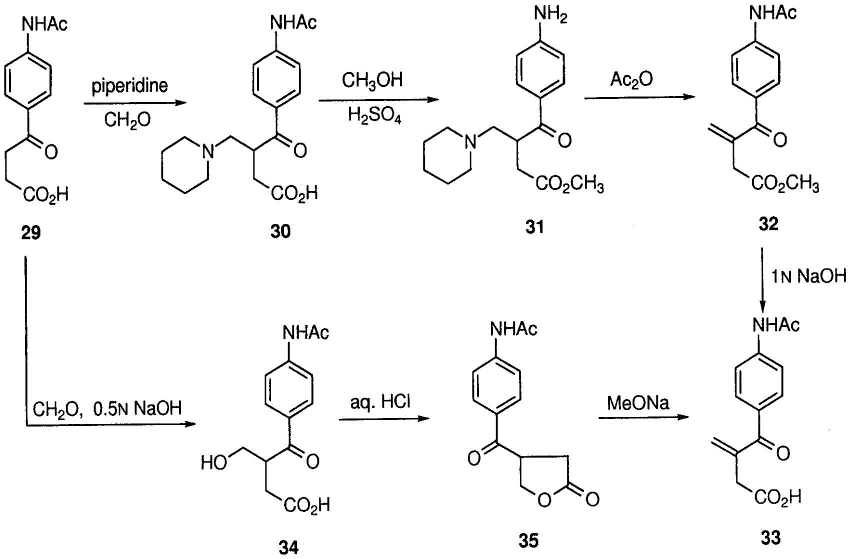


Chart 6

retention times of 8.0 and 14.1 min, corresponding to the (*R*)- and (*S*)-isomers, respectively. The absolute configuration of **6** was confirmed by conversion of **6** to the known chiral anilino-pyridazinone (**8**).[3]

Hydrogenation of 3-(4-acetamidobenzoyl)crotonic acid (**10**) using (*R*)-**5** conveniently gave the corresponding butyric acid [(*S*)-**6**] with 76% ee, while (*S*)-**5** gave (*R*)-**6** with 79% ee. On the other hand, hydrogenation of the isocrotonic acid (**28**) using (*R*)-**5** gave (*R*)-**6** with 46% ee, even though the procedure was the same as in the case of **10**. Hydrogenation of the corresponding β,γ-unsaturated carboxylic acid (**33**) in the presence of (*S*)-**5** at 100 atm occurred with no enantioselectivity at all and that at 10 atm gave (*R*)-**6** with 30% ee. Thus, the asymmetric induction largely depended upon the substitution pattern, including double-bond geometry, as noted in the literature.[6b)]

It was reported that hydrogenation of ethyl 4-chloro-3-oxobutanoate using 0.05 mol% of (*S*)-**5** quantitatively gave the corresponding (3*R*)-alcohol with 97% ee within a few minutes under 100 atm at 100 °C.[16)] On the other hand, hydrogenation of **10** using 0.25 mol% of (*S*)-**5** quantitatively afforded (*R*)-**6** with 55% ee, while the use of 2 mol% of the catalyst improved the selectivity to 73% ee. Hydrogenation of the *N*-carbobenzyloxy and *N*-*tert*-butoxycarbonyl derivatives (**14** and **16**) gave the corresponding 3-aroylbutyric acids (**20** and **22**), respectively, with about the same enantioselectivity as in the *N*-acetyl case (**10**), suggesting that the substituent at the aniline nitrogen had little influence on the stereoselectivity in the hydrogenation, as was expected from the literature[6b)] (Table 1).

We also examined reduction of the olefinic double bond in the γ-keto unsaturated esters (**11**, **27** and **32**) using chiral ruthenium diiodide 2,2′-diphenylphosphino-binaphthyl complex [(*S*)-**36**][17)] as follows (Table 1): Methyl 3-aroylisocrotonate (**27**) resisted hydrogenation even under drastic conditions of 100 °C and 100 atm. The reaction mixture was purified by preparative TLC to afford (*R*)-**18** in 38% yield with 6% ee. The lactone (**37**) and the allyl alcohol (**38**) were obtained as by-products in 4% and 30% yields, respectively (Chart 7). Each structure was confirmed by means of spectral analyses. In the NMR spectrum of **37**, a pair of doublet methyl proton signals at δ 0.69 and 1.16 appeared in a ratio of about 1 : 2

indicating **37** to be a mixture of two diastereomers.

Methyl 3-aroylcrotonate (**11**) also resisted hydrogenation, like **27**, probably due to steric hindrance to coordination of the catalyst. Purification by preparative TLC gave (*S*)-**18** in 59% yield with 29% ee and two by-products, the lactone (**37**) and methyl 3-aroylisocrotonate (**27**). The latter compound (**27**) was formed probably through transition metal complex-catalyzed olefin isomerization of thermodynamically less stable **11**.[18]

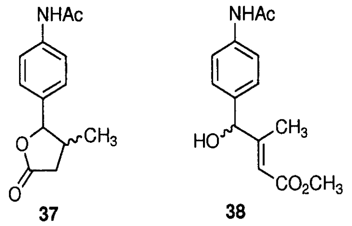


Chart 7

In contrast to **11** and **27**, the β-methylidene-γ-keto ester (**32**) was quantitatively hydrogenated under 5 atm of hydrogen at room temperature to (*R*)-**18** with 65% ee in the opposite sense to compound **11**.

Conversion of **6** to Chiral Diaminopyridazinones (**2**): Both enantiomers of 3-(4-acetamidobenzoyl)butyric acid (**6**) were transformed to the corresponding chiral diaminopyridazinones (**2**) as follows (Charts 8 and 9). Cyclization of (*R*)-**6** with equimolar hydrazine acetate gave the corresponding pyridazinone [(*R*)-**7**] in 93% yield without racemization. Then (*R*)-**7** was deprotected by heating with excess hydrazine acetate to give the anilino-pyridazinone [(*R*)-**8**] in 66% yield with 99% ee. Similarly, the pyridazinone [(*S*)-**7**] was obtained from (*S*)-**6** in 90% yield with 99% ee. Then deprotection of (*S*)-**7** with hydrazine acetate gave (*S*)-**8** in 61% yield with 99% ee.

Using the same method as for the racemate synthesis[1] (Chart 9), (*R*)-**8** was linked reductively at the aniline

Table 1. Asymmetric Hydrogenation of 3-Aroylbutenoic Acid Derivatives

Substrate[a]	Catalyst	S/C[b]	H_2 (atm)	Temperature (°C)	Time (h)	Product[c]	Yield (%)	Optical yield[d] (% ee)	Configuration
10	(*R*)-**5**	400	100	r.t.	48	**6**	100	76	*S*
10	(*S*)-**5**	400	100	r.t.	48	**6**	100	79	*R*
10	(*S*)-**5**	400	75	100[e]	5[f]	**6**	100	55	*R*
10	(*S*)-**5**	50	115	100[e]	3[f]	**6**	100	73	*R*
14	(*S*)-**5**	400	100	r.t.	96	**20**	100	74[g]	*R*
16	(*S*)-**5**	400	80	r.t.	48	**22**	100	79[h]	*R*
28	(*R*)-**5**	400	130	r.t.	48	**6**	100	37	*R*
28	(*R*)-**5**	120	130	r.t.	48	**6**	100	46	*R*
33	(*S*)-**5**	400	100	r.t.	16	**6**	100	5	*R*
33	(*S*)-**5**	400	10	r.t.	48	**6**	100	30	*R*
11	(*S*)-**36**	400	100	100[e]	3	**18**	59	29	*S*
27	(*S*)-**36**	400	100	100[e]	3	**18**	38	6	*R*
32	(*S*)-**36**	400	80	r.t.	48	**18**	100	50	*R*
32	(*S*)-**36**	400	10	r.t.	72	**18**	100	64	*R*
32	(*S*)-**36**	200	5	r.t.	72	**18**	100	65	*R*

a) The structures are shown in Charts 3, 5 and 6. *b*) Substrate/catalyst. *c*) The structures are shown in Chart 4. *d*) The enantiomeric excess was determined by HPLC analysis. *e*) Ethanol was used as a solvent. *f*) min. *g*) $[\alpha]_D^{26}$ +8.8° (c=1.00, EtOH). *h*) $[\alpha]_D^{27}$ +7.8° (c=1.00, EtOH).

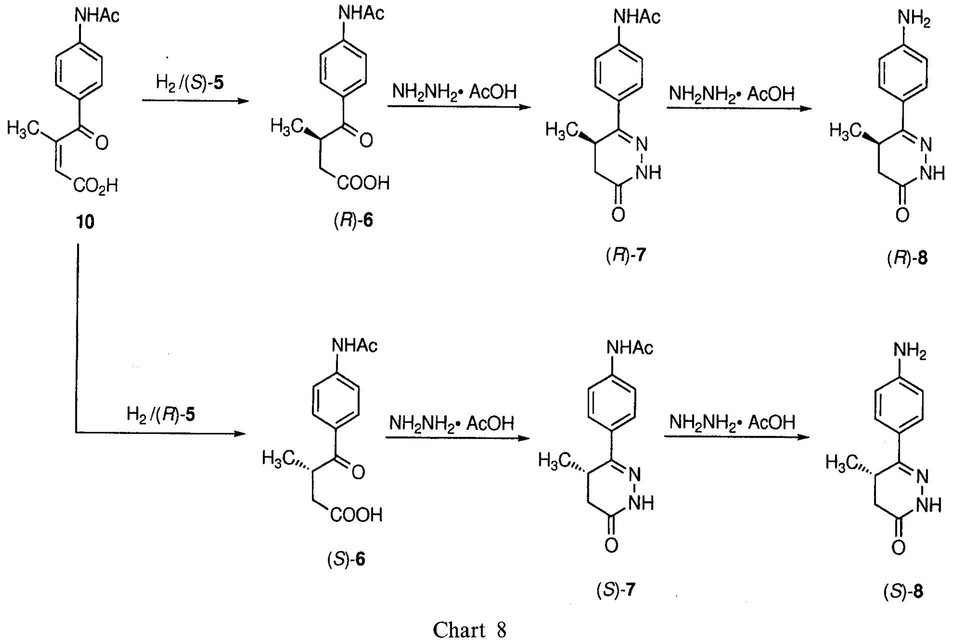


Chart 8

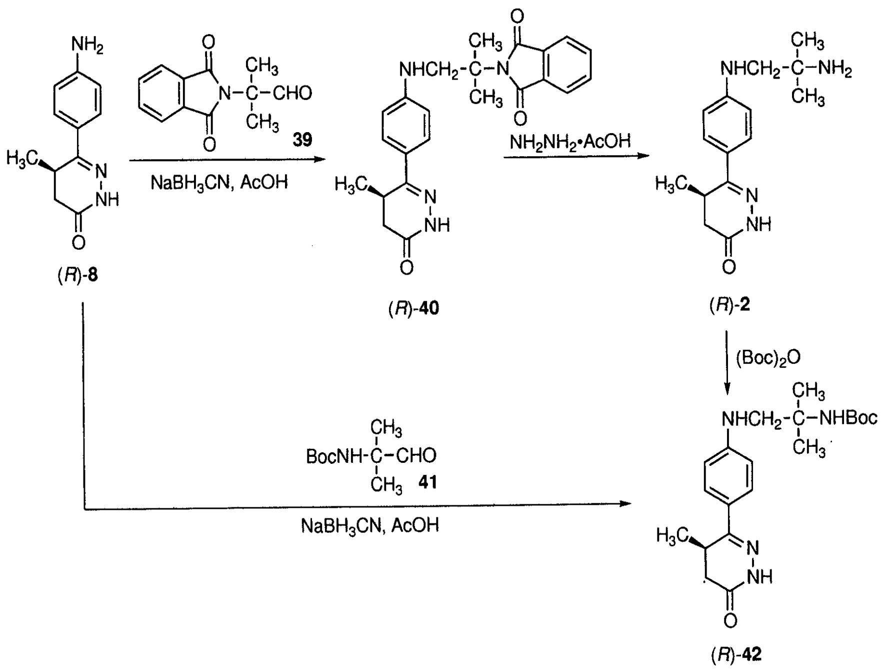


Chart 9

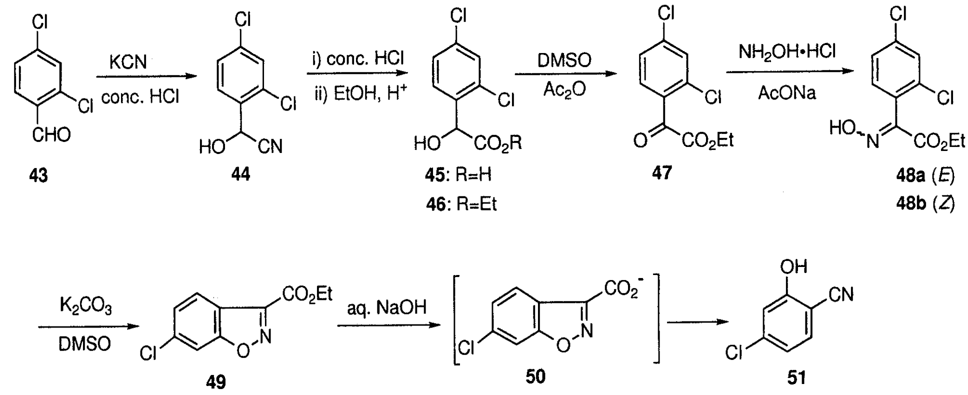


Chart 10

nitrogen with 2-methyl-2-phthaliminopropanal (**39**)[1,19] to afford (*R*)-**40** in 63% yield with 98% ee.[20] Then deprotection of (*R*)-**40** with hydrazine acetate smoothly proceeded to give (*R*)-**2** in 86% yield without loss of the optical purity. Treatment of (*R*)-**2** with excess di-*tert*-butyl dicarbonate gave the carbamate [(*R*)-**42**], which was identical with an authentic sample obtained by reductive *N*-alkylation of (*R*)-**8** with the *N*-Boc-protected aminoaldehyde (**41**).[1] Similarly (*S*)-diaminopyridazinone [(*S*)-**2**] was derived from the corresponding anilinopyridazinone [(*S*)-**8**] in 59% yield.

Preparation of Chiral Glycidyl Ether (3) Synthesis of 5-Chloro-2-cyanophenol (**51**): 5-Chloro-2-cyanophenol (**51**) was obtained from 2,4-dichlorobenzaldehyde (**43**) as follows (Chart 10). Compound **43** was converted to the corresponding cyanohydrin (**44**) in the usual way and subsequent hydrolysis gave the α-hydroxy acid (**45**). After esterification, oxidation of the ester (**46**) with dimethyl sulfoxide (DMSO) and acetic anhydride[21] gave the α-keto ester (**47**). Treatment of **47** with hydroxylamine hydrochloride in the presence of sodium acetate afforded the *E*-oxime (**48a**) as a major product, accompanied with a small amount of the *Z*-isomer (**48b**). The configuration of the C = N double bond in each oxime was determined from the NMR spectra, in which the signals of the hydroxy proton of **48a** and **48b** were seen at δ 9.80 and 12.06, respectively. In addition, **48b** showed a higher *Rf* value on TLC than **48a**, indicating formation of intramolecular hydrogen bonding between the hydroxy group and the carbonyl oxygen in **48b**.

Cyclization of **48a** with potassium carbonate in DMSO gave the benzisoxazole (**49**). According to the reported method,[22] treatment of **49** with aqueous sodium hydroxide gave the phenol (**51**) in an overall yield of 66% from **48a**. When a solution of **48** in DMSO was treated with potassium hydroxide in a one-pot procedure, avoiding isolation of the base-sensitive benzisoxazole intermediate (**49**, **50**), **51** was conveniently obtained in 88% yield.

Conversion of **51** to Chiral Glycidyl Ethers (**3**): The phenol (**51**) was enantioselectively transformed to (*R*)-glycidyl ethers [(*R*)-**3**] as follows (Chart 11). (*R*)-1-Tosyloxy-2,3-propanediol acetonide [(*R*)-**52**][23] was unequivocally obtained from D-mannitol.[24] According to the reported method,[25] *O*-alkylation of the phenol (**51**)

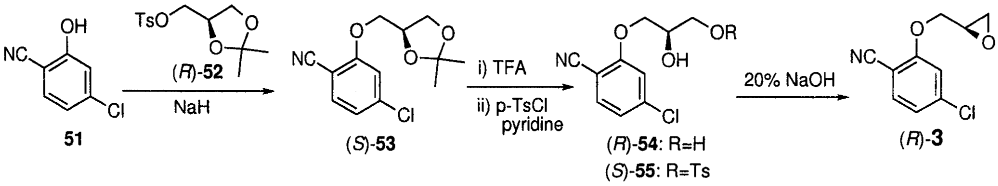


Chart 11

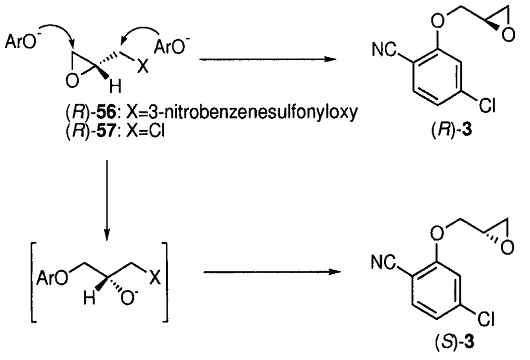


Chart 12

with the tosylate [(*R*)-**52**] in the presence of sodium hydride gave the aryl ether [(*S*)-**53**]. After deprotection with trifluoroacetic acid, the resulting diol [(*R*)-**54**] was easily converted to the monotosylate [(*S*)-**55**] with *p*-toluenesulfonyl chloride in pyridine. Treatment of (*S*)-**55** with sodium hydroxide gave the (*R*)-glycidyl ether [(*R*)-**3**] with 85% ee in an overall yield of 33% from **51**.

The reaction of **51** with (*R*)-glycidyl 3-nitrobenzenesulfonate [(*R*)-**56**] gave (*R*)-**3** with 93% ee, as was expected from the finding of Sharpless *et al.* that reaction of **56** with a variety of phenoxides proceeded in a direct displacement of the arenesulfonate group with the phenoxide anion (Chart 12).[26a)] Similarly (*S*)-**3** was derived from (*S*)-**56** with 93% ee (Table 2).

On the other hand, the reaction of **51** with (*R*)-epichlorohydrin [(*R*)-**57**][27)] in acetone under reflux in the presence of potassium carbonate resulted predominantly in epoxide ring opening[26)] to give (*S*)-**3** with 80% ee. When the reaction was carried out at 120 °C with no solvent or potassium carbonate, the intermediate chlorohydrin [(*R*)-**58**] was obtained in an excellent yield (Chart 13). Without purification, a solution of (*R*)-**58** in toluene was treated with aqueous sodium hydroxide in the presence of a catalytic amount of benzyltriethylammonium chloride[28)] to give the (*S*)-glycidyl ether [(*S*)-**3**] in 79% yield with 95% ee (Table 2). The optical purity was raised to over 99% ee by recrystallization from ethanol. The chlorohydrin [(*R*)-**58**] was easily derived from (*S*)-**3** with hydrochloric acid. Similarly the reaction of **51** with (*S*)-**57**, followed by treatment with aqueous sodium hydroxide gave (*R*)-**3** in 86% yield with 98% ee. Thus, the nucleophilic substitution reaction at 120 °C proceeded at the terminal carbon atom of the epoxide ring with high regioselectivity, probably *via* activating complexation (**59**) as presumed by McClure *et al.*[26b)]

Preparation of the Optical Isomers of TZC-5665 (1) The four optical isomers (**1a**—**d**) were unequivocally prepared by the reaction of chiral diaminopyridazinone (**2**) with chiral glycidyl ether (**3**). The optical purity of each of **1a**—**d** was about 99% based upon HPLC using an ovomucoid- or a pepsin-bound silica column (Fig. 1).

Pharmacology

The hypotensive and β-blocking activities of TZC-5665 (**1**) and the optical isomers (**1a**—**d**) were examined in anesthetized rats using the procedures previously described.[29)] The inhibitory activity on PDE III, isolated from left ventricular tissues of dogs, was also tested using a modification of the procedure described by Thompson and Appleman.[2,30)] The results are shown in Table 3.

Hypotensive Activity In decreasing blood pressure, the (R_A,S_B)- and (R_A,R_B)-isomers (**1c** and **1d**) were about 2 times more potent than racemic **1**, while the (S_A,S_B)-isomer (**1a**) was one-fifth as potent as the (R_A,S_B)-isomer (**1c**), and the (S_A,R_B)-isomer (**1b**) was one-tenth as potent as the (R_A,R_B)-isomer (**1d**). Thus, the hypotensive activity was in the following order: (R_A,S_B)- $=$ (R_A,R_B)- > racemic **1** > (S_A,S_B)- > (S_A,R_B)-isomer. According to the report of Slater *et al.*,[3,31)] compound **60**, in which a betoxalol-like aryloxypropanolamine moiety is combined with the anilino-pyridazinone (**8**) through a propionamido-spacer link, showed antihypertensive activity when the asymmetric carbon atom of the pyridazinone ring had (*R*)-configuration. This was also the case for the optical isomers of **1**.

In our previous study on phenoxypropanolamine derivatives having a hydrazinopyridazinyl moiety on the *N*-alkyl substituent, the stereochemistry of the phenoxypropanolamine moiety seemed to have no influence on the hypotensive activity.[32)] Similarly the (R_A,S_B)- and (R_A,R_B)-isomers (**1c** and **1d**) both showed about 2 times more potent hypotensive activity than **1**. On the other hand, in the case of inactive (S_A)-pyridazinones (**1a** and **1b**), the stereochemistry of the phenoxypropanolamine moiety appeared to be significant for the hypotensive activity. Thus, the (S_A,S_B)-isomer (**1a**), having a (*S*)-phenoxypropanolamine moiety showed 2 times more potent hypotensive activity than the (S_A,R_B)-isomer (**1b**).

β-Blocking Activity It is well known that (*S*)-configuration at the C-2 position in an aryloxypropanolamine β-blocker is essential for β-blocking activity.[33)] Indeed, the compounds having a (*S*)-phenoxypropanolamine moiety (**1a** and **1c**) showed potent β-blocking activities. The β-blocking activity was in the following order: (S_A,S_B)- > racemic **1** ≧ (R_A,S_B)- > (S_A,R_B)- > (R_A,R_B)-isomer. This order is the same as that of another phenoxypropanolamine derivative (**60**).[3)]

It was reported that in the case of labetalol (**61**), an arylethanolamine α,β-blocker possessing two asymmetric centers, only the (*R*,*R*)-isomer (dilevalol) among the four

Table 2. Synthesis of Chiral Glycidyl Ether (**3**)

Compound No.	Solvent	Base	Temperature (°C)	Time (h)	Yield (%)	Optical yield[a] (% ee)	Configuration
(*R*)-**56**	DMF	NaH	r.t.	22	85	93	*R*
(*S*)-**56**	DMF	NaH	r.t.	22	85	93	*S*
(*R*)-**57**	Acetone	K_2CO_3	Reflux	48	69	80	*S*
(*R*)-**57**	Neat	—	120	2	79[b]	95	*S*
(*S*)-**57**	Neat	—	120	2	86[b]	98	*R*

a) The enantiomeric excess was determined by HPLC analysis. *b*) Overall yield *via* the chlorohydrin (**58**).

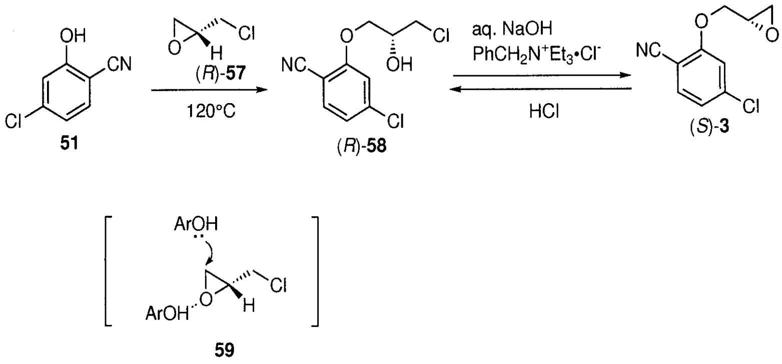


Chart 13

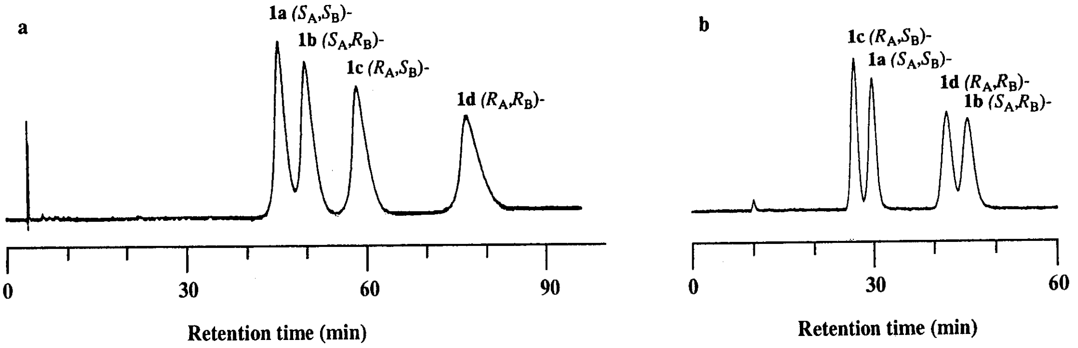


Fig. 1. Elution Patterns of TZC-5665 (**1**) from (a) a ULTRON ES-OVM Column with 20 mM HCO_2NH_4–CH_3CN (1000 : 42) at a Flow Rate of 1.0 ml/min and (b) a ULTRON ES-PEPSIN Column with 20 mM HCO_2NH_4 (pH 5.0)–EtOH (5 : 1) at a Flow Rate of 0.3 ml/min

The chromatographic conditions were as described in Experimental.

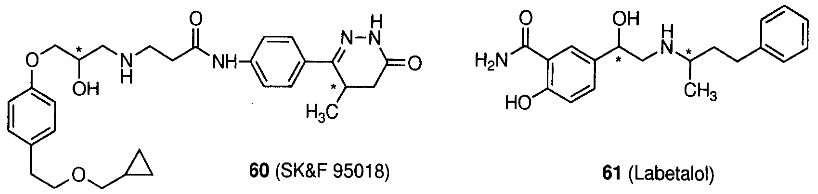
optical isomers showed β-blocking activity.[34] On the other hand, in the case of **1**, the stereochemistry of the *N*-alkyl substituent in the phenoxypropanolamine moiety seemed to exert little influence on the β-blocking activity, probably due to the relatively large distance between the nitrogen atom and the pyridazinone ring.

PDE III-Inhibitory Activity The PDE III-inhibitory activity, as well as the hypotensive activity, of **1** was observed when the asymmetric carbon atom on the pyridazinone moiety was in (*R*)-configuration. This finding is in accordance with previous reports on chiral pyridazinone derivatives.[5,35] In inhibiting PDE III activity, the (R_A,S_B)-isomer (**1c**) was 1.4 times more potent than racemic **1**, while the (R_A,R_B)-isomer (**1d**) was 2.5 times more potent than racemic **1**. On the other hand, the (S_A,S_B)- (**1a**) and (S_A,R_B)-isomers (**1b**) were 120 times less and 30 times less potent than racemic **1**, respectively. The (R_A,R_B)-isomer (**1d**) was 300 times more potent than the (S_A,S_B)-isomer (**1a**). Thus, the PDE III-inhibitory activity was in the following order: (R_A,R_B)- > (R_A,S_B)- > racemic **1** > (S_A,R_B)- > (S_A,S_B)-isomer.

Table 3. Pharmacological Activities of TZC-5665 (**1**) and Its Optical Isomers (**1a**—**d**)

Compound No.		β-Blocking activity[a]		Hypotensive activity[b]		PDE III-inhibitory activity[c]	
		Mean±S.E.	(*n*)	Mean	(*n*)	Mean	(*n*)
	Racemic **1**	55.6±3.2	(5)	37.2	(5)	0.21	(2)
1a	(S_A,S_B)-**1**	41.9±2.2	(5)	29.4[d]	(5)	25.8	(2)
1b	(S_A,R_B)-**1**	251.7±51.8	(5)	16.8[d]	(5)	6.98	(2)
1c	(R_A,S_B)-**1**	60.2±2.8	(5)	50	(5)	0.15	(2)
1d	(R_A,R_B)-**1**	467.7±103.0	(5)	50	(5)	0.084	(2)

Each compound was injected intravenously into anesthetized rats. β-Blocking activities were evaluated as antagonism of isoproterenol (0.1 μg/kg i.v.)-induced tachycardia. Hypotensive activities were determined by measuring the decrease in arterial blood pressure at 10 min after administration when the compounds (0.1—1 mg/kg) were cumulatively injected at 10 min intervals. PDE III-inhibitory activity was measured using a modification of the procedure described by Thompson and Appleman.[30] *a*) Dose (μg/kg i.v.) giving 50% inhibition of tachycardia. *b*) Degree of hypotension (mmHg) at a dose of 1 mg/kg. *c*) Concentration (μM) of drug reducing the basal PDE III activity to 50%. *d*) The compounds (0.3—3 mg/kg) were cumulatively injected. *n*, number of experiments.



60 (SK&F 95018)

61 (Labetalol)

Chart 14

Conclusion

The four optical isomers of TZC-5665 (**1**) were synthesized by reacting chiral diaminopyridazinone (**2**) with chiral glycidyl ether (**3**). Chiral **2** was obtained by means of the following reaction sequence: asymmetric hydrogenation of 3-aroylcrotonic acid (**10**) to chiral 3-aroylbutyric acid (**6**) with high enantioselectivity, cyclization of chiral **6** with hydrazine acetate to the corresponding anilino-pyridazinone (**8**) without racemization, and reductive alkylation of **8**. Chiral glycidyl ether (**3**) was obtained by heating a mixture of the phenol (**51**) and (*R*)- or (*S*)-epichlorohydrin (**57**). Thus, by using these procedures, each optical isomer of **1** was obtained in an adequate amount for pharmacological studies.

The hypotensive and PDE III-inhibitory activity of each optical isomer of **1** appeared when the asymmetric carbon atom on the pyridazinone moiety was in (*R*)-configuration, and the β-blocking activity appeared when the asymmetric carbon atom on the phenoxypropanolamine moiety was in (*S*)-configuration. Among the four optical isomers of TZC-5665 (**1**), the (R_A,S_B)-isomer (**1c**) seemed to be the best as regards hypotensive, β-blocking and PDE III-inhibitory activities.

Experimental

Melting points were determined with a Mettler FP-2 melting point apparatus and are uncorrected. NMR spectra were taken at 90 MHz on a Hitachi R-90H spectrometer with tetramethylsilane as an internal standard. IR spectra were measured with a Perkin–Elmer 1640 FT-IR spectrophotometer. Mass spectra were determined with a Shimadzu GCMS-QP 1000 instrument. All compounds were analyzed for C, H, and N, and the results were within ±0.3% of the theoretical values. Specific rotations were measured on a JASCO DPI-140 digital polarimeter. HPLC was performed on a Hitachi HPLC instrument (L-6000 pump, L-3000 photodiode array detector and D-2500 chromato-integrator) using the following conditions, unless otherwise stated: column, Chiralcel OD (Daicel Chemical Industry); mobile phase, *n*-hexane–iso-PrOH (4 : 1); flow rate, 1.0 ml/min; detector, UV absorption at 300 nm; room temperature. TLC was performed on Merck Kieselgel 60 F_{254} TLC plates. Column chromatography was carried out on silica gel (Waco gel C-200). The optical purity was determined by HPLC analysis using a chiral stationary phase.

3-(4-Acetamidobenzoyl)crotonic Acid (10) *N*,*N*-Dimethylformamide (DMF) (4.6 ml, 58.4 mmol) was added dropwise to $AlCl_3$ (27.8 g, 0.21 mol) with stirring at room temperature. After the exothermic reaction ceased, acetanilide (**9**) (2.84 g, 21 mmol) and citraconic anhydride (2.35 g, 21 mmol) were added portionwise to the mixture at 70 °C with stirring. Stirring was continued for 3 h at 70 °C, then the whole was poured onto ice and extracted three times with AcOEt. The combined organic layer was washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. Chromatography of the residue on a silica gel column with $CHCl_3$–MeOH (40 : 1) gave **10** (1.87 g, 34% yield) as colorless crystals, mp 190—193 °C (lit.[8] mp 132.5—135 °C). NMR (CD_3OD) δ: 1.94 (3H, d, $J=1.5$ Hz), 2.12 (3H, s), 5.94 (1H, q, $J=1.5$ Hz), 7.61 (4H, s). IR (KBr): 3298, 1712, 1650, 1595, 1532 cm^{-1}. MS *m*/*z*: 247 (M^+), 162, 120 (base peak). *Anal.* Calcd for $C_{13}H_{13}NO_4 \cdot 0.5H_2O$: C, 60.93; H, 5.51; N, 5.47. Found: C, 60.92; H, 5.48; N, 5.49.

Methyl 3-(4-Acetamidobenzoyl)crotonate (11) A solution of **10** (3.0 g, 12.1 mmol) in 25% methanolic HCl (30 ml) was stirred for 2 h with ice-cooling and then evaporated under reduced pressure. The residue was recrystallized from C_6H_6 to give **11** (2.92 g, 92% yield) as colorless crystals, mp 136—139 °C. NMR ($CDCl_3$) δ: 2.12 (3H, d, $J=1.5$ Hz), 2.17 (3H, s), 3.58 (3H, s), 6.02 (1H, q, $J=1.5$ Hz), 7.51 (2H, d, $J=9$ Hz), 7.50—7.90 (1H, m), 7.80 (2H, d, $J=9$ Hz). IR (KBr): 3320, 3282, 1715, 1697, 1658, 1596, 1528 cm^{-1}. MS *m*/*z*: 261 (M^+), 162, 120 (base peak). *Anal.* Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.41; H, 5.61; N, 5.36.

Ethyl 3-(4-Aminobenzoyl)crotonate (12) A solution of **10** (5.0 g, 20.2 mmol) in 20% ethanolic HCl (90 ml) was stirred for 24 h at room temperature and then evaporated under reduced pressure. The residue was dissolved in H_2O. The solution was alkalinized with aqueous $NaHCO_3$. The separated oily material was extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. Chromatography of the residue on a silica gel column with $CHCl_3$ gave **12** (4.47 g, 95% yield) as pale yellow crystals. An analytical sample was obtained by recrystallization from EtOH, mp 79—82 °C. NMR ($CDCl_3$) δ: 1.26 (3H, t, $J=7$ Hz), 1.88 (3H, d, $J=1.5$ Hz), 3.53 (2H, q, $J=7$ Hz), 3.75 (2H, br s), 5.81 (1H, q, $J=1.5$ Hz), 6.65 (2H, d, $J=9$ Hz), 7.22 (2H, d, $J=9$ Hz). IR (KBr): 3444, 3358, 1738, 1635, 1611, 1521 cm^{-1}. MS *m*/*z*: 233 (M^+), 188, 120 (base peak). *Anal.* Calcd for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48; N, 6.01. Found: C, 66.66; H, 6.39; N, 6.01.

3-[4-(Benzyloxycarbonylamino)benzoyl]crotonic Acid (14) Benzyl chloroformate (4.0 ml, 28 mmol) was added dropwise to a stirred solution of **12** (4.47 g, 19.2 mmol) in DMF (50 ml) with ice-cooling. Stirring was continued for 2 h at room temperature, then the solution was poured into ice-water. The separated oily material was extracted with AcOEt. The organic layer was washed three times with H_2O, dried over $MgSO_4$ and evaporated under reduced pressure. Chromatography of the residue on a silica gel column with $CHCl_3$–MeOH (100 : 1) gave **13** (4.44 g, 63% yield) as a pale yellow viscous oil. NMR ($CDCl_3$) δ: 1.28 (3H, t, $J=7$ Hz), 1.87 (3H, d, $J=1.5$ Hz), 3.54 (2H, q, $J=7$ Hz), 5.20 (2H, s), 5.85 (1H, q, $J=1.5$ Hz), 6.74 (1H, br s), 7.37 (4H, s), 7.40 (5H, s). MS *m*/*z*: 367 (M^+), 91 (base peak).

A solution of **13** (4.44 g, 12.1 mmol) and 1 N NaOH (14.5 ml, 14.5 mmol) in EtOH (80 ml) was stirred for 1 h at room temperature and then evaporated under reduced pressure. The residue was dissolved in H_2O. The whole was acidified with 1 N HCl (20 ml, 20 mmol) and extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was recrystallized from Et_2O–iso-Pr_2O to give **14** (2.96 g, 72% yield) as colorless crystals, mp 158—159 °C. NMR ($CDCl_3$) δ: 1.95 (3H, s), 5.19 (2H, s), 5.82 (1H, br s), 6.80—7.80 (1H, m), 7.00 (1H, br s), 7.37 (9H, s). IR (KBr): 3363, 2949, 1734, 1689, 1658, 1639, 1590, 1528, 1216 cm^{-1}. MS *m*/*z*: 339 (M^+), 295, 146, 91 (base peak). *Anal.* Calcd for $C_{19}H_{17}NO_5$: C, 67.25; H, 5.05; N, 4.13. Found: C, 66.99; H, 4.85; N, 4.18.

3-[4-(*tert*-Butoxycarbonylamino)benzoyl]crotonic Acid (16) A solution of **12** (4.7 g, 20.2 mmol) and $(Boc)_2O$ (6.6 g, 30.3 mmol) in $CHCl_3$ (100 ml) was stirred for 8 d at room temperature and evaporated under reduced pressure. Chromatography of the residue on a silica gel column with C_6H_6 gave **15** (4.58 g, 68% yield) as a colorless viscous oil. NMR ($CDCl_3$) δ: 1.27 (3H, t, $J=7$ Hz), 1.52 (9H, s), 1.87 (3H, d, $J=2$ Hz), 3.57 (2H, q, $J=7$ Hz), 5.84 (1H, q, $J=2$ Hz), 6.53 (1H, br s), 7.37 (4H, s). MS *m*/*z*: 333 (M^+), 277, 57 (base peak).

In the same manner as described for the synthesis of **14**, compound **16** (2.91 g, 65% yield) was prepared from **15** (4.58 g, 13.8 mmol). An analytical sample was obtained by recrystallization from iso-Pr_2O as colorless crystals, mp 137—138 °C. NMR ($CDCl_3$) δ: 1.52 (9H, s), 1.97 (3H, br s), 5.84 (1H, br s), 6.77 (1H, br s), 7.00—7.63 (5H, m). IR (KBr): 3345, 2983, 1732, 1688, 1653, 1637, 1596, 1584, 1229, 1154 cm^{-1}. MS *m*/*z*: 305 (M^+), 120, 57 (base peak). *Anal.* Calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.84; H, 6.17; N, 4.63.

Methyl 3-(4-Acetamidobenzoyl)butyrate (18) Methyl 3-(4-aminobenzoyl)butyrate (**17**) was prepared by the method of McEvoy and Allen.[9] Acetic anhydride (9.6 ml, 96.2 mmol) was added dropwise to a stirred solution of **17** (15.0 g, 67.9 mmol) in pyridine (75 ml) with ice-cooling. The mixture was stirred for 4 h at room temperature, then poured into ice-water. The resulting precipitate was collected by filtration and recrystallized from C_6H_6–*n*-hexane to give **18** (15.75 g, 88% yield) as colorless crystals, mp 123—124 °C (lit.[13] mp 122—124 °C). NMR ($CDCl_3$) δ: 1.22 (3H, d, $J=7$ Hz), 2.20 (3H, s), 2.44 (1H, dd, $J=17$, 6 Hz), 2.96 (1H, dd, $J=17$, 8 Hz), 3.64 (3H, s), 3.70—4.15 (1H, m), 7.54 (1H, br s), 7.60 (2H, d, $J=9$ Hz), 7.96 (2H, d, $J=9$ Hz). IR (KBr): 3313, 1733, 1674, 1599, 1539, 1248 cm^{-1}. MS *m/z*: 263 (M^+), 232, 162 (base peak), 120.

HPLC of the racemic **18** using a chiral stationary phase gave two peaks of (*R*)- and (*S*)-**18** at the retention times of 8.0 and 14.1 min, respectively. The absolute configuration of each isomer was identified from that of the known chiral **8**.

Methyl 3-[4-(Benzyloxycarbonylamino)benzoyl]butyrate (19) In the same manner as described for the synthesis of **13**, compound **19** (803 mg, 50% yield) was prepared from **17** (1.0 g, 4.52 mmol). An analytical sample was obtained by recrystallization from iso-Pr_2O as colorless crystals, mp 77—78 °C. NMR ($CDCl_3$) δ: 1.21 (3H, d, $J=7$ Hz), 2.42 (1H, dd, $J=16$, 5 Hz), 2.95 (1H, dd, $J=16$, 8 Hz), 3.64 (3H, s), 3.70—4.05 (1H, m), 5.22 (2H, s), 6.92 (1H, br s), 7.20—7.50 (5H, m), 7.47 (2H, d, $J=9$ Hz), 7.95 (2H, d, $J=9$ Hz). IR (KBr): 3320, 1746, 1718, 1666, 1592, 1537, 1210 cm^{-1}. MS *m/z*: 355 (M^+), 324, 146 (base peak). *Anal.* Calcd for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.47; H, 5.93; N, 3.94.

HPLC of the racemic **19** using a chiral stationary phase gave two peaks of (*R*)- and (*S*)-**19** at the retention times of 20.5 and 33.5 min, respectively. The absolute configuration of each isomer was identified from that of the known chiral **8**.

3-[4-(Benzyloxycarbonylamino)benzoyl]butyric Acid (20) In the same manner as described for the synthesis of **14**, compound **19** (800 mg, 2.25 mmol) was treated with 1 N NaOH to give **20** (620 mg, 81% yield) as colorless crystals, mp 123—125 °C. NMR ($CDCl_3$) δ: 1.20 (3H, d, $J=7$ Hz), 2.43 (1H, dd, $J=16$, 5 Hz), 3.00 (1H, dd, $J=16$, 8 Hz), 3.64 (3H, s), 3.55—4.30 (1H, m), 5.25 (2H, s), 7.00—7.70 (3H, m), 7.42 (5H, s), 7.95 (2H, d, $J=8$ Hz), 8.80 (1H, br s). IR (KBr): 3344, 3034, 1734, 1706, 1664, 1586, 1527, 1220 cm^{-1}. MS *m/z*: 341 (M^+), 254, 91 (base peak). *Anal.* Calcd for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C,66.62; H, 5.55; N, 4.09.

Methyl 3-[4-(*tert*-Butoxycarbonylamino)benzoyl]butyrate (21) A solution of **17** (1.0 g, 4.52 mmol) and $(Boc)_2O$ (2.0 g, 9.2 mmol) in $CHCl_3$ (30 ml) was refluxed for 30 h with stirring and worked up as described for **15** to give **21** (1.073 g, 74% yield). An analytical sample was obtained by recrystallization from iso-Pr_2O as colorless needles, mp 95—97 °C. NMR ($CDCl_3$) δ: 1.21 (3H, d, $J=7$ Hz), 1.53 (9H, s), 2.42 (1H, dd, $J=16$, 6 Hz), 2.94 (1H, dd, $J=16$, 8 Hz), 3.64 (3H, s), 3.60—4.10 (1H, m), 6.69 (1H, br s), 7.45 (2H, d, $J=9$ Hz), 7.95 (2H, d, $J=8$ Hz). IR (KBr): 3340, 1732, 1716, 1674, 1602, 1585, 1523, 1411, 1233, 1153 cm^{-1}. MS *m/z*: 321 (M^+), 57 (base peak). *Anal.* Calcd for $C_{17}H_{23}NO_5$: C, 63.53; H, 7.21; N, 4.36. Found: C, 63.42; H, 7.25; N, 4.54.

HPLC of the racemic **21** using a chiral stationary phase gave two peaks of (*R*)- and (*S*)-**21** at the retention times of 5.5 and 8.5 min, respectively. The absolute configuration of each isomer was identified from that of the known chiral **8**.

3-[4-(*tert*-Butoxycarbonylamino)benzoyl]butyric Acid (22) In the same manner as described for the synthesis of **14**, compound **22** (600 mg, 78% yield) was prepared from **21** (800 mg, 2.49 mmol). Colorless crystals, mp 152—154 °C. NMR ($CDCl_3$) δ: 1.23 (3H, d, $J=7$ Hz), 1.54 (9H, s), 2.45 (1H, dd, $J=16$, 6 Hz), 3.02 (1H, dd, $J=16$, 8 Hz), 3.60—4.20 (1H, m), 7.24 (1H, br s), 7.47 (2H, d, $J=8$ Hz), 7.99 (2H, d, $J=8$ Hz), 9.15 (1H, br s). IR (KBr): 3327, 2981, 1730, 1708, 1666, 1593, 1535, 1234, 1157 cm^{-1}. MS *m/z*: 307 (M^+), 251, 57 (base peak). *Anal.* Calcd for $C_{16}H_{21}NO_5$: C, 62.52; H, 6.89; N, 4.56. Found: C, 62.42; H, 6.89; N, 4.53.

3-(4-Acetamidobenzoyl)-2-hydroxybutyric Acid (24) A solution of glyoxylic acid monohydrate (15.64 g, 0.17 mol) in 1 N NaOH (180 ml, 0.18 mol) was added dropwise to a stirred solution of 4-acetamidopropiophenone (**23**) (19.1 g, 0.1 mol) and benzyltriethylammonium chloride (227 mg, 1.0 mmol) in MeOH (400 ml) at room temperature. The mixture was stirred for 6 h, then MeOH was removed under reduced pressure. The residue was acidified with 2 N HCl (120 ml, 0.24 mol) and extracted three times with AcOEt. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was stirred overnight and the resulting precipitate was collected by filtration to give **24** (15.67 g, 59% yield) as colorless crystals, mp 201—205 °C. NMR (CD_3OD) δ: 1.22 (3H, d, $J=7$ Hz), 2.15 (3H, s), 3.75—4.25 (1H, m), 4.48 (1H, d, $J=5$ Hz), 7.69 (2H, d, $J=9$ Hz), 7.95 (2H, d, $J=9$ Hz). IR (KBr): 3512, 2938, 1735, 1664, 1582, 1540, 1213 cm^{-1}. MS *m/z*: 265 (M^+), 247, 191, 162 (base peak), 120. *Anal.* Calcd for $C_{13}H_{15}NO_5 \cdot 0.1H_2O$: C, 58.46; H, 5.74; N, 5.25. Found: C, 58.52; H, 5.63; N, 5.11.

Methyl 3-(4-Acetamidobenzoyl)-2-hydroxybutyrate (25) A solution of **24** (12.0 g, 45.3 mmol) in 25% methanolic HCl (60 ml) was stirred for 2 h with ice-cooling and evaporated under reduced pressure. The residue was triturated with iso-Pr_2O to give **25** (8.78 g, 70% yield) as colorless crystals, mp 109—114 °C. NMR ($CDCl_3$) δ: 1.28, 1.36 (3H, two d, $J=7$ Hz), 2.21 (3H, s), 3.29 (1H, d, $J=4$ Hz), 3.60—4.10 (1H, m), 3.70, 3.80 (3H, two s), 4.25—4.67 (1H, m), 7.50 (1H, br s), 7.62 (2H, d, $J=9$ Hz), 7.91, 7.93 (2H, two d, $J=9$ Hz). MS *m/z*: 279 (M^+), 191, 162 (base peak), 120. IR (KBr): 3185, 1750, 1674, 1597, 1540 cm^{-1}. *Anal.* Calcd for $C_{14}H_{17}NO_5$: C, 60.20; H, 6.14; N, 5.02. Found: C, 60.08; H, 6.08; N, 5.06.

Methyl 3-(4-Acetamidobenzoyl)isocrotonate (27) Methanesulfonyl chloride (10.8 g, 94.3 mmol) was added dropwise to a stirred solution of **25** (13.15 g, 47.1 mmol) and Et_3N (14.27 g, 0.141 mol) in $CHCl_3$ (130 ml) with ice-cooling. The mixture was stirred for 30 min, then H_2O was added to it. The organic layer was washed with H_2O, dried over $MgSO_4$ and evaporated under reduced pressure. Chromatography of the residue on a silica gel column with $CHCl_3$ gave **26** (14.06 g, 81% yield) as a colorless viscous oil. NMR ($CDCl_3$) δ: 1.25, 1.36 (3H, two d, $J=7$ Hz), 2.21 (3H, s), 3.06, 3.17 (3H, two s), 3.83—4.18 (1H, m), 3.76, 3.83 (3H, two s), 5.26, 5.43 (1H, two d, $J=8$, 6 Hz), 7.56 (1H, br s), 7.63 (2H, d, $J=9$ Hz), 7.91 (2H, d, $J=9$ Hz). MS *m/z*: 357 (M^+), 162 (base peak), 120.

A solution of **26** (10.72 g, 9.2 mmol) and DBU (5.46 g, 35.9 mmol) in C_6H_6 (300 ml) was refluxed for 1 h with stirring. After cooling, the solution was washed with H_2O, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was recrystallized from C_6H_6 to give **27** (6.31 g, 83% yield) as colorless crystals, mp 110—112 °C. NMR ($CDCl_3$) δ: 2.22 (3H, s), 2.40 (3H, d, $J=1.5$ Hz), 3.77 (3H, s), 6.11 (1H, q, $J=1.5$ Hz), 7.55 (1H, s), 7.61 (2H, d, $J=9$ Hz), 7.81 (2H, d, $J=9$ Hz). IR (KBr): 3351, 1726, 1701, 1638, 1585 cm^{-1}. MS *m/z*: 261 (M^+), 162, 120 (base peak). *Anal.* Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.19; H, 5.71; N, 5.44.

3-(4-Acetamidobenzoyl)isocrotonic Acid (28) In the same manner as described for the synthesis of **14**, compound **28** (3.78 g, 63% yield) was prepared from **27** (6.3 g, 24.1 mmol). Recrystallization from AcOEt gave colorless crystals, mp 205—208 °C. NMR (CD_3OD) δ: 2.15 (3H, s), 2.34 (3H, d, $J=1.5$ Hz), 6.06 (1H, q, $J=1.5$ Hz), 7.69 (2H, d, $J=9$ Hz), 7.82 (2H, d, $J=9$ Hz). IR (KBr): 3328, 1695, 1646, 1583, 1262 cm^{-1}. MS *m/z*: 247 (M^+), 162, 120 (base peak). *Anal.* Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67. Found: C, 63.11; H, 5.33; N, 5.56.

3-(4-Acetamidobenzoyl)-3-butenoic Acid (33) Method A: Compound **32** was prepared by the method of Mitchell *et al.*[13] A solution of **32** (3.0 g, 11.5 mmol) and 1 N NaOH (12 ml, 12 mmol) in iso-PrOH (30 ml) was stirred for 1 h at room temperature and worked up as described for **14**. Recrystallization from AcOEt gave **33** (1.22 g, 43% yield) as colorless crystals, mp 131—134 °C. NMR (CD_3OD) δ: 2.15 (3H, s), 3.51 (2H, s), 5.71 (1H, s), 5.99 (1H, s), 7.55—7.87 (4H, m). IR (KBr): 3346, 2911, 1707, 1652, 1594, 1532, 1205 cm^{-1}. MS *m/z*: 247 (M^+), 162, 120 (base peak). *Anal.* Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67. Found: C, 62.90; H, 5.33; N, 5.56.

Method B: According to a reported method,[15] 37% formaldehyde (4.2 ml, 56.1 mmol) was added dropwise to a stirred solution of **29** (12.0 g, 51 mmol) in 0.5 N NaOH (112 ml, 56 mmol) at room temperature. The mixture was stirred for 6 h, then acidified with concentrated HCl (5.6 ml, 65.2 mmol). The whole was stirred overnight at room temperature. The resulting precipitate was collected by filtration and recrystallized from AcOEt to give **35** (8.674 g, 69% yield) as colorless crystals, mp 154—157 °C (lit.[14] mp 152—154 °C). NMR (CD_3OD) δ: 2.12 (3H, s), 2.60—2.93 (2H, m), 4.30—4.80 (3H, m), 7.65 (2H, d, $J=9$ Hz), 7.90 (2H, d, $J=9$ Hz). IR (KBr): 3320, 1762, 1696, 1667, 1599, 1535 cm^{-1}. MS *m/z*: 247 (M^+).

A solution of **35** (2.47 g, 10 mmol) and $NaOCH_3$ (0.54 g, 10 mmol) in MeOH (25 ml) was stirred for 15 min at room temperature, then neutralized with 2 N HCl (5 ml, 10 mmol) and evaporated under reduced pressure. H_2O was added to the residue and the whole was extracted with AcOEt. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. After standing overnight, the resulting precipitate was collected by filtration to give **33** (1.48 g, 60% yield) as colorless crystals, which were identical with those obtained by method A.

General Procedure of Catalytic Hydrogenation (*R*)- and (*S*)-BINAP were prepared from β-naphthol according to the method reported by Takaya *et al.*[36] The specific rotations were as follows: (*R*)-BINAP $[\alpha]_D^{24}$ +229° (c=0.31, toluene), (*S*)-BINAP $[\alpha]_D^{25}$ −232° (c=0.30, toluene) [lit.[36a] (*R*)-BINAP $[\alpha]_D^{25}$ +229° (c=0.32, C_6H_6), (*S*)-BINAP $[\alpha]_D^{25}$ −229° (c=0.31, C_6H_6)]. They were converted to the corresponding chiral catalysts (**5** and **36**, respectively) according to the method described by Noyori *et al.*[6,17]

A 0.3 M solution of a substrate in MeOH was hydrogenated in a stainless steel autoclave in the presence of 0.25 mol% of a chiral catalyst (**5** or **36**). After disappearance of the substrate was confirmed by TLC, the solution was evaporated under reduced pressure. Chromatography of the residue on a silica gel column gave the reduction product. The optical purities of 3-aroylbutyric acid (**6**, **20** and **22**) were determined by HPLC of the corresponding methyl esters (**18**, **19** and **21**) using a chiral stationary phase. The absolute configuration of each isomer was assigned by comparison with the optical isomers of **8**. The results are shown in Table 1.

Hydrogenation of 11 Hydrogenation of **11** (645 mg, 2.47 mmol) in MeOH (20 ml) using (*S*)-**36** (6 mg) was carried out at 100 °C under 100 atm for 3 h. The solution was evaporated under reduced pressure. Preparative TLC of the residue with Et_2O gave the starting material **11** (110 mg, 17% yield), methyl 3-aroylisocrotonate (**27**) (57 mg, 9% yield), methyl (*S*)-3-aroylbutyrate [(*S*)-**18**] (384 mg, 59% yield) with 29% ee and γ-(4-acetamidophenyl)-β-methyl-γ-butyrolactone (**37**) (18 mg, 3% yield).

γ-(4-Acetamidophenyl)-β-methyl-γ-butyrolactone (**37**): Colorless crystals, mp 137—149 °C. NMR ($CDCl_3$) δ: 0.69, 1.16 (3H, two d, J=7 Hz), 2.10—2.95 (3H, m), 2.16 (3H, s), 4.95, 5.55 (1H, two d, J=8 Hz), 7.22 (2H, d, J=9 Hz), 7.53 (2H, d, J=9 Hz), 7.92 (1H, br s). IR (KBr): 3252, 2964, 1793, 1662, 1607, 1555 cm^{-1}. MS m/z: 233 (M^+), 121 (base peak). *Anal.* Calcd for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48; N, 6.01. Found: C, 66.88; H, 6.40; N, 5.94.

Hydrogenation of 27 In the same manner as described above, compound **27** (550 mg, 2.11 mmol) was hydrogenated using (*S*)-**36** as the catalyst. Preparative TLC of the residue with Et_2O gave the starting material **27** (88 mg, 16% yield), methyl (*R*)-3-aroylbutyrate [(*R*)-**18**] (212 mg, 38% yield) with 6% ee, γ-(4-acetamidophenyl)-β-methyl-γ-butyrolactone (**37**) (18 mg, 4% yield) and methyl (2*E*)-4-acetamidophenyl-4-hydroxy-3-methylbutenoate (**38**) (164 mg, 30% yield).

Methyl (2*E*)-4-Acetamidophenyl-4-hydroxy-3-methylbutenoate (**38**): Colorless crystals, mp 54—57 °C. NMR ($CDCl_3$) δ: 1.96 (3H, d, J=1 Hz), 2.00—2.40 (1H, m), 2.15 (3H, s), 3.72 (3H, s), 5.09 (1H, br s), 6.25 (1H, q, J=1 Hz), 7.10—7.70 (1H, m), 7.26 (2H, d, J=9 Hz), 7.46 (2H, d, J=9 Hz). IR (KBr): 3515, 3252, 1700, 1661, 1605, 1155, 1058 cm^{-1}. MS m/z: 263 (M^+), 169, 122 (base peak). *Anal.* Calcd for $C_{14}H_{17}NO_4 \cdot 0.75\ H_2O$: C, 60.74; H, 6.74; N, 5.06. Found: C, 60.63; H, 6.45; N, 4.95.

(*R*)-(+)-3-(4-Acetamidobenzoyl)butyric Acid [(*R*)-6] A solution of **10** (35.0 g, 0.126 mol) and (*S*)-**5** (292 mg, 0.347 mmol) in dry MeOH (470 ml) was hydrogenated under 80 atm for 48 h at room temperature. After the disappearance of **10** was confirmed by TLC [$CHCl_3$–MeOH–AcOH (40 : 2 : 1)], the solution was evaporated under reduced pressure. Chromatography of the residue on a silica gel column with $CHCl_3$–MeOH (100 : 1) quantitatively gave crude (*R*)-**6** (35.21 g, 79% ee). Recrystallization from AcOEt gave (*R*)-**6** (22.91 g, 65% yield) as colorless crystals, mp 144—145 °C. NMR (CD_3OD) δ: 1.18 (3H, d, J=7 Hz), 2.15 (3H, s), 2.41 (1H, dd, J=16, 5 Hz), 2.85 (1H, dd, J=16, 8 Hz), 3.67—4.15 (1H, m), 7.69 (2H, d, J=9 Hz), 7.97 (2H, d, J=9 Hz). IR (KBr): 3379, 3339, 2964, 1700, 1654, 1593, 1520 cm^{-1}. MS m/z: 249 (M^+), 162 (base peak), 120. *Anal.* Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.50; H, 5.97; N, 5.55. $[\alpha]_D^{20}$ +13.9° (c=1.00, EtOH). The optical purity was 99% ee on HPLC. t_R 7.9 min

(*S*)-(−)-3-(4-Acetamidobenzoyl)butyric Acid [(*S*)-6] In the same manner as described above, crude (*S*)-**6** (36.04 g, 76% ee) was quantitatively prepared from **10** (35.75 g, 0.145 mol) using (*R*)-**5** (148 mg, 0.176 mmol) as the catalyst. Recrystallization from AcOEt gave (*S*)-**6** (21.20 g, 60% yield) as colorless crystals, mp 144—145 °C. The NMR, IR and mass spectra of (*S*)-**6** were identical with those of (*R*)-**6**. *Anal.* Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.45; H, 5.92; N, 5.83. $[\alpha]_D^{20}$ −14.7° (c=1.00, EtOH). The optical purity was 99% ee on HPLC. t_R 13.9 min.

(*R*)-(−)-6-(4-Acetamidophenyl)-4,5-dihydro-5-methylpyridazin-3(2*H*)-one [(*R*)-7] A solution of (*R*)-**6** (10.0 g, 40.2 mmol) obtained above and hydrazine acetate (4.43 g, 48.2 mmol) in EtOH (150 ml) was refluxed for 30 min with stirring and evaporated under reduced pressure. H_2O was added to the residue and the precipitate was collected by filtration, washed with H_2O and dried *in vacuo*. The filtrate was extracted with $CHCl_3$ and the organic layer was treated as described below. Recrystallization of the precipitate from MeOH gave (*R*)-**7** (9.153 g, 93% yield) as colorless prisms, mp 228—230 °C. NMR (DMSO-d_6) δ: 1.08 (3H, d, J=7 Hz), 2.05 (3H, s), 2.22 (1H, br d, J=16 Hz), 2.66 (1H, dd, J=16, 7 Hz), 3.07—3.56 (1H, m), 7.58 (2H, d, J=9 Hz), 7.72 (2H, d, J=9 Hz), 10.00 (1H, s), 10.80 (1H, s). IR (KBr): 3214, 1670, 1590, 1532 cm^{-1}. MS m/z: 245 (M^+), 203, 188, 118. *Anal.* Calcd for $C_{13}H_{15}N_3O_2$: C, 63.66; H, 6.16; N, 17.13. Found: C, 63.65; H, 6.12; N, 17.00. $[\alpha]_D^{20}$ −448.9° (c=1.00, DMF). The optical purity was 99% ee on HPLC [column, Chiralcel OJ (Daicel Chemical Industry); mobile phase, *n*-hexane–iso-PrOH (7 : 3)]. t_R 11.2 min.

The aforementioned $CHCl_3$ layer was dried over $MgSO_4$ and evaporated under reduced pressure. Chromatography of the residue on a silica gel column with $CHCl_3$ gave (*R*)-**8** (221 mg, 3% yield) as colorless crystals. The optical purity was 97% ee on HPLC [mobile phase, *n*-haxane–iso-PrOH (7 : 3)]. t_R 22.4 min.

(*S*)-(+)-6-(4-Acetamidophenyl)-4,5-dihydro-5-methylpyridazin-3(2*H*)-one [(*S*)-7] In the same manner as described above, (*S*)-**7** (19.30 g, 90% yield) was prepared from (*S*)-**6** (21.86 g, 87.8 mmol) obtained above. Recrystallization from MeOH gave colorless prisms, mp 230—232 °C. The NMR, IR and mass spectra of (*S*)-**7** were identical with those of (*R*)-**7**. *Anal.* Calcd for $C_{13}H_{15}N_3O_2$: C, 63.66; H, 6.16; N, 17.13. Found: C, 63.68; H, 6.05; N, 16.99. $[\alpha]_D^{20}$ +446.9° (c=1.00, DMF). The optical purity was 99% ee on HPLC [the same conditions as above]. t_R 17.9 min.

When the crude (*S*)-**6** (6.0 g, 24 mmol, 75% ee) was used, (*S*)-**7** (4.07 g) was obtained in 69% yield with 79% ee. Crude (*S*)-**7** (4.07 g) was dissolved in MeOH (40 ml) and the solution was stirred overnight. The deposited racemic **7** was removed by filtration. The filtrate was concentrated under reduced pressure and stored overnight to give (*S*)-**7** (2.60 g, 64% yield) with 99% ee as colorless crystals.

(*R*)-(−)-6-(4-Aminophenyl)-4,5-dihydro-5-methylpyridazin-3(2*H*)-one [(*R*)-8] A solution of (*R*)-**7** (12.57 g, 51.3 mmol) obtained above and hydrazine acetate (46.92 g, 0.51 mol) in MeOH (230 ml) was refluxed for 48 h with stirring under a nitrogen atmosphere and evaporated under reduced pressure. H_2O was added to the residue and the precipitate was collected by filtration. Recrystallization from EtOH gave (*R*)-**8** (6.83 g, 66% yield) as colorless needles, mp 210—212 °C. NMR (DMSO-d_6) δ: 1.04 (3H, d, J=7 Hz), 2.15 (1H, dd, J=17, 1 Hz), 2.60 (1H, dd, J=17, 6 Hz), 3.03—3.47 (1H, m), 5.42 (2H, s), 6.57 (2H, d, J=9 Hz), 7.47 (2H, d, J=9 Hz), 10.60 (1H, s). IR (KBr): 3454, 3329, 3213, 1663 cm^{-1}. MS m/z: 203 (M^+), 188, 118. *Anal.* Calcd for $C_{11}H_{13}N_3O$: C, 65.01; H, 6.45; N, 20.68. Found: C, 64.79; H, 6.32; N, 20.40. $[\alpha]_D^{20}$ −582.4° (c=1.00, DMF). [lit.[3] $[\alpha]_D^{25}$ −539.4° (c=0.94, DMF)]. The optical purity was 99% ee on HPLC [mobile phase, *n*-hexane–iso-PrOH (7 : 3)]. t_R 22.4 min.

(*S*)-(+)-6-(4-Aminophenyl)-4,5-dihydro-5-methylpyridazin-3(2*H*)-one [(*S*)-8] In the same manner as described above, (*S*)-**7** (2.0 g, 8.16 mmol) obtained above was converted to crude (*S*)-**8** (1.36 g, 82% yield, 96% ee). Two recrystallization from EtOH gave (*S*)-**8** (1.01 g, 61% yield) as colorless needles, mp 211—212 °C. The NMR, IR and mass spectra of (*S*)-**8** were identical with those of (*R*)-**8**. *Anal.* Calcd for $C_{11}H_{13}N_3O$: C, 65.01; H, 6.45; N, 20.68. Found: C, 64.79; H, 6.30; N, 20.42. $[\alpha]_D^{20}$ +580.4° (c=1.00, DMF). [lit.[3] $[\alpha]_D^{25}$ +560.0° (c=0.95, DMF)]. The optical purity was 99% ee on HPLC [the same conditions as above]. t_R 28.6 min.

(*R*)-(−)-6-[4-(2-Methyl-2-phthaliminopropylamino)phenyl]-4,5-dihydro-5-methylpyridazin-3(2*H*)-one [(*R*)-40] A mixture of (*R*)-**8** (6.23 g, 30.7 mmol) obtained above, 2-methyl-2-phthaliminopropanal (**39**) (8.0 g, 36.9 mmol), AcOH (2.21 g, 36.8 mmol) and dry MeOH (100 ml) was stirred for 30 min at room temperature. Then a solution of $NaBH_3CN$ (966 mg, 15.6 mmol) in dry MeOH (10 ml) was added dropwise to the resulting yellow solution with stirring. The mixture was stirred overnight at room temperature and the precipitate was collected by filtration. Recrystallization from acetone gave (*R*)-**40** (7.83 g, 63% yield) as yellow crystals, mp 234—236 °C. NMR ($CDCl_3$) δ: 1.18 (3H, d, J=7 Hz), 1.76 (6H, s), 2.35 (1H, dd, J=17, 2 Hz), 2.66 (1H, dd, J=17, 7 Hz), 3.07—3.37

(1H, m), 3.63—3.84 (2H, br s), 4.30—4.60 (1H, br s), 6.62 (2H, d, $J=9$ Hz), 7.52 (2H, d, $J=9$ Hz), 7.60—7.86 (4H, m), 8.39 (1H, br s). IR (KBr): 3374, 3198, 1771, 1706, 1684 cm^{-1}. MS *m/z*: 404 (M$^+$). *Anal.* Calcd for $C_{23}H_{24}N_4O_3$: C, 68.30; H, 5.98; N, 13.85. Found: C, 68.11; H, 5.83; N, 13.69. $[\alpha]_D^{20}$ $-308.4°$ ($c=1.00$, $CHCl_3$). The optical purity was 98% ee on HPLC [column, chiral stationary phase in which (*R*)-(−)-*N*-(3,5-dinitrobenzoyl)phenylglycine was bounded ionically to γ-aminopropylsilica[20] (250×4.6 mm i.d.); mobile phase, CH_2Cl_2–iso-PrOH (100:1)]. t_R 31.4 min.

(*S*)-(+)-6-[4-(2-Methyl-2-phthaliminopropylamino)phenyl]-4,5-dihydro-5-methylpyridazin-3(2*H*)-one [(*S*)-40] In the same manner as described above, (*S*)-**40** (12.10 g, 66% yield) was prepared from (*S*)-**8** (9.28 g, 45.7 mmol) obtained above. Recrystallization from acetone gave yellow crystals, mp 235—237 °C. The NMR, IR and mass spectra of (*S*)-**40** were identical with those of (*R*)-**40**. *Anal.* Calcd for $C_{23}H_{24}N_4O_3$: C, 68.30; H, 5.98; N, 13.85. Found: C, 68.05; H, 5.91; N, 13.67. $[\alpha]_D^{20}$ $+307.6°$ ($c=1.00$, $CHCl_3$). The optical purity was 98% ee on HPLC [the same conditions as above]. t_R 40.9 min.

(*R*)-(−)-6-[4-(2-Amino-2-methylpropylamino)phenyl]-4,5-dihydro-5-methylpyridazin-3(2*H*)-one [(*R*)-2] A mixture of (*R*)-**40** (11.07 g, 27.4 mmol) obtained above, hydrazine acetate (12.61 g, 0.137 mol) and EtOH (130 ml) was refluxed for 3 h with stirring. After cooling, the resulting precipitate was removed by filtration. The filtrate was evaporated under reduced pressure and the residue was dissolved in H_2O. The solution was alkalinized with K_2CO_3 and the separated oily material was extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was recrystallized from EtOH to give (*R*)-**2** (6.436 g, 86% yield) as colorless needles, mp 186—188 °C. NMR (CD_3OD) δ: 1.15 (3H, d, $J=7$ Hz), 1.16 (6H, s), 2.29 (1H, dd, $J=17$, 2 Hz), 2.69 (1H, dd, $J=17$, 7 Hz), 3.06 (2H, s), 3.10—3.65 (1H, m), 6.67 (2H, d, $J=9$ Hz), 7.58 (2H, d, $J=9$ Hz). IR (KBr): 3329, 3266, 1652, 1610 cm^{-1}. MS *m/z*: 274 (M$^+$). *Anal.* Calcd for $C_{15}H_{22}N_4O$: C, 65.66; H, 8.08; N, 20.42. Found: C, 65.68; H, 8.10; N, 20.17. $[\alpha]_D^{20}$ $-427.3°$ ($c=1.00$, EtOH). A solution of (*R*)-**2** (1 mg) and $(Boc)_2O$ (10 mg) in CH_2Cl_2 (5 ml) was stirred for 48 h at room temperature and directly subjected to HPLC [column, Chiralcel OJ (Daicel Chemical Industry); mobile phase, *n*-hexane–iso-PrOH (7:3)]. The optical purity was 98% ee. t_R 13.7 min. The retention time of the resulting carbamate was identical with that of (*R*)-**42** obtained from (*R*)-**8** and **41** as described below.

(*S*)-(+)-6-[4-(2-Amino-2-methylpropylamino)phenyl]-4,5-dihydro-5-methylpyridazin-3(2*H*)-one [(*S*)-2] In the same manner as described above, (*S*)-**2** (7.366 g, 90% yield) was prepared from (*S*)-**40** (12.1 g, 30 mmol) obtained above. Recrystallization from EtOH gave colorless needles, mp 186—188 °C. The NMR, IR and mass spectra of (*S*)-**2** were identical with those of (*R*)-**2**. *Anal.* Calcd for $C_{15}H_{22}N_4O$: C, 65.66; H, 8.08; N, 20.42. Found: C, 65.36; H, 8.20; N, 20.41. $[\alpha]_D^{20}$ $+422.1°$ ($c=1.00$, EtOH). The optical purity was 98% ee on HPLC [the same conditions as above]. t_R 20.4 min.

(*R*)-(−)-6-[4-(2-*tert*-Butoxycarbonylamino-2-methylpropylamino)phenyl]-4,5-dihydro-5-methylpyridazin-3(2*H*)-one [(*R*)-42] By the same method as used for the synthesis of the racemate,[1] a solution of (*R*)-**8** (406 mg, 2 mmol) obtained above, 2-*tert*-butoxycarbonylamino-2-methylpropanal (**41**) (486 mg, 2.6 mmol) and AcOH (120 mg, 2 mmol) in MeOH (10 ml) was treated with $NaBH_3CN$ (63 mg, 1 mmol). The reaction mixture was evaporated under reduced pressure and the residue was dissolved in $CHCl_3$. The solution thus obtained was washed with 5% Na_2CO_3, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified on a silica gel column with $CHCl_3$. Recrystallization of the product from iso-Pr_2O gave (*R*)-**42** (654 mg, 88% yield) as colorless crystals, mp 150—152 °C. NMR ($CDCl_3$) δ: 1.22 (3H, d, $J=7$ Hz), 1.34 (6H, s), 1.42 (9H, s), 2.18—2.95 (2H, m), 3.05—3.55 (1H, m), 3.31 (2H, s), 4.58 (1H, br s), 6.58 (2H, d, $J=9$ Hz), 7.52 (2H, d, $J=9$ Hz), 8.59 (1H, br s). IR (KBr): 3341, 1701, 1660, 1644, 1611 cm^{-1}. MS *m/z*: 374 (M$^+$), 216, 58 (base peak). *Anal.* Calcd for $C_{20}H_{30}N_4O_3$: C, 64.14; H, 8.07; N, 14.96. Found: C, 64.13; H, 8.19; N, 15.00. $[\alpha]_D^{20}$ $-325.9°$ ($c=1.00$, EtOH). The optical purity was 99.5% ee on HPLC [column, Chiralcel OJ (Daicel Chemical Industry); mobile phase, *n*-hexane–iso-PrOH (7:3)]. t_R 13.7 min.

(*S*)-(+)-6-[4-(2-*tert*-Butoxycarbonylamino-2-methylpropylamino)phenyl]-4,5-dihydro-5-methylpyridazin-3(2*H*)-one [(*S*)-42] In the same manner as described above, (*S*)-**42** (613 mg, 82% yield) was prepared from (*S*)-**8** (406 mg, 2 mmol) obtained above. Recrystallization from iso-Pr_2O gave colorless crystals, mp 151—152 °C. The NMR, IR and mass spectra of (*S*)-**42** were identical with those of (*R*)-**42**. *Anal.* Calcd for $C_{20}H_{30}N_4O_3$: C, 64.14; H, 8.07; N, 14.96. Found: C, 64.15; H, 8.19; N, 14.68. $[\alpha]_D^{20}$ $+327.5°$ ($c=1.00$, EtOH). The optical purity was 99.5% ee on HPLC [the same conditions as above]. t_R 20.4 min.

α-Hydroxy-2,4-dichlorophenylacetonitrile (44) Concentrated HCl (110 ml, 1.28 mol) was added dropwise over a period of 2 h to a mixture of 2,4-dichlorobenzaldehyde (**43**) (210 g, 1.2 mol), KCN (85.8 g, 1.32 mol) and AcOEt (700 ml) at 20—25 °C with vigorous stirring. The whole was stirred for 1 h at room temperature, then AcOEt (200 ml) was added. The organic layer was washed three times with brine, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was dissolved in *n*-hexane (200 ml) and stirred overnight. The resulting precipitate was collected by filtration to give **44** (169.7 g, 70% yield) as pale yellow crystals, mp 96—100 °C. NMR ($CDCl_3$) δ: 3.01 (1H, s), 5.82 (1H, s), 7.36 (1H, dd, $J=9$, 2 Hz), 7.47 (1H, d, $J=2$ Hz), 7.67 (1H, d, $J=9$ Hz). IR (KBr): 3446, 2246 cm^{-1}. MS *m/z*: 203 (M$^+$+2), 201 (M$^+$), 76 (base peak). *Anal.* Calcd for $C_8H_5Cl_2NO$: C, 47.56; H, 2.49; N, 6.93. Found: C, 47.59; H, 2.40; N, 7.00.

α-Hydroxy-2,4-dichlorophenylacetic Acid (45) A solution of **44** (31.7 g, 0.157 mol) in 6 N HCl (45 ml, 0.27 mol) was refluxed for 2 h with stirring. The solution was poured into ice-water (200 ml) and the whole was kept cool for 2 h with stirring. The resulting precipitate was collected by filtration, washed with H_2O and dried to give **45** (33.75 g, 97% yield) as colorless crystals. An analytical sample was obtained by recrystallization from *n*-hexane–Et_2O, mp 120—121 °C. NMR ($CDCl_3$) δ: 5.10—6.30 (2H, m), 5.61 (1H, s), 7.10—7.36 (2H, m), 7.42 (1H, s). IR (KBr): 3443, 3089, 1750, 1716, 1518 cm^{-1}. MS *m/z*: 222 (M$^+$+2), 220 (M$^+$), 175 (base peak). *Anal.* Calcd for $C_8H_6Cl_2O_3$: C, 43.47; H, 2.74. Found: C, 43.35; H, 2.68.

Ethyl α-Hydroxy-2,4-dichlorophenylacetate (46) A solution of **45** (33.75 g, 0.153 mol) and H_2SO_4 (1.0 ml) in EtOH (60 ml) was refluxed overnight with stirring, then cooled and evaporated under reduced pressure. The residue was dissolved in AcOEt (60 ml). The solution thus obtained was washed three times with H_2O, dried over $MgSO_4$ and evaporated under reduced pressure to give **46** (36.19 g, 95% yield) as a colorless liquid, which was sufficiently pure for analysis. NMR ($CDCl_3$) δ: 1.22 (3H, t, $J=7$ Hz), 3.63 (1H, d, $J=5$ Hz), 4.22, 4.23 (2H, two q, $J=7$ Hz), 5.50 (1H, d, $J=5$ Hz), 7.10—7.50 (3H, m). IR (liq. film): 3458, 1737, 1590, 1188 cm^{-1}. MS *m/z*: 250 (M$^+$+2), 248 (M$^+$), 175 (base peak). *Anal.* Calcd for $C_{10}H_{10}Cl_2O_3$: C, 48.22; H, 4.05. Found: C, 47.92; H, 3.99.

Ethyl α-Keto-2,4-dichlorophenylacetate (47) Acetic anhydride (15.9 ml, 0.168 mol) was added dropwise over a period of 1 h to a stirred solution of **46** (36.19 g, 0.145 mol) in DMSO (38 ml) at 90 °C. Stirring was continued for 1 h at 90 °C. After the mixture had cooled, H_2O (10 ml) and AcOEt (60 ml) were added to the reaction mixture. The organic layer was washed three times with brine, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by vacuum distillation to give **47** (33.77 g, 90% yield) as a pale yellow oil, bp 130—147 °C (0.5 mmHg). NMR ($CDCl_3$) δ: 1.40 (3H, t, $J=7$ Hz), 4.42 (2H, q, $J=7$ Hz), 7.25—7.55 (2H, m), 7.73 (1H, d, $J=9$ Hz). IR (liq. film): 1737, 1698, 1582, 1199 cm^{-1}. MS *m/z*: 248 (M$^+$+2), 246 (M$^+$), 173 (base peak). *Anal.* Calcd for $C_{10}H_8Cl_2O_3$: C, 48.61; H, 3.26. Found: C, 48.41; H, 3.42.

Ethyl α-Hydroxyimino-2,4-dichlorophenylacetate (48) A mixture of **47** (33.77 g, 0.137 mol), hydroxylamine hydrochloride (10.53 g, 0.15 mol), anhydrous AcONa (12.18 g, 0.151 mol) and EtOH (40 ml) was stirred for 2 h at room temperature. The precipitate was removed by filtration. The filtrate was evaporated under reduced pressure and H_2O was added to the residue. The resulting precipitate was collected by filtration to give **48** (35.82 g) quantitatively. This was used for the preparation of **51** without further purification. Recrystallization from iso-Pr_2O gave **48a** as colorless needles, mp 106—109 °C. NMR ($CDCl_3$) δ: 1.29 (3H, t, $J=7$ Hz), 4.32 (2H, q, $J=7$ Hz), 7.21 (1H, d, $J=9$ Hz), 7.34 (1H, dd, $J=9$, 2 Hz), 7.47 (1H, d, $J=2$ Hz), 9.80 (1H, br s). IR (KBr): 3320, 1716, 1626, 1587 cm^{-1}. MS *m/z*: 263 (M$^+$+2), 261 (M$^+$), 226 (base peak), 198, 180. *Anal.* Calcd for $C_{10}H_9Cl_2NO_3$: C, 45.83; H, 3.46; N, 5.34. Found: C, 45.69; H, 3.43; N, 5.41. The mother liquor was evaporated under reduced pressure. Chromatography of the residue on a silica gel column with *n*-hexane–AcOEt (5:1) gave **48b** as a pale brown oil. NMR ($CDCl_3$) δ: 1.30 (3H, t, $J=7$ Hz), 4.36 (2H, q, $J=7$ Hz), 7.20—7.50 (3H, m), 12.06 (1H, s). MS *m/z*: 263 (M$^+$+2), 261 (M$^+$), 226, 198, 180 (base peak).

Ethyl 6-Chlorobenzisoxazole-3-carboxylate (49) A mixture of **48a**

(6.0 g, 22.9 mmol), K_2CO_3 (3.16 g, 22.9 mmol) and DMSO (30 ml) was stirred for 30 min at 100 °C. After the mixture had cooled, H_2O (150 ml) was added to it. The resulting precipitate was collected by filtration, washed with H_2O and dried *in vacuo*. Recrystallization from *n*-hexane gave **49** (3.73 g, 73% yield) as colorless crystals, mp 63—64 °C. NMR ($CDCl_3$) δ: 1.49 (3H, t, $J=7$ Hz), 4.56 (2H, q, $J=7$ Hz), 7.42 (1H, dd, $J=9$, 2 Hz), 7.69 (1H, dd, $J=2$, 1 Hz), 8.05 (1H, dd, $J=9$, 1 Hz). IR (KBr): 1725 cm^{-1}. MS *m/z*: 227 ($M^+ + 2$), 225 (M^+), 180, 153 (base peak). *Anal.* Calcd for $C_{10}H_8ClNO_3$: C, 53.23; H, 3.57; N, 6.21. Found: C, 53.05; H, 3.47; N, 6.06.

5-Chloro-2-cyanophenol (51) Method A: A solution of **49** (2.25 g, 10 mmol) and 1 N NaOH (11 ml, 11 mmol) in EtOH (50 ml) was refluxed for 30 min with stirring. After cooling, the solution was evaporated under reduced pressure and H_2O (10 ml) was added to the residue. The whole was acidified with 1 N HCl (12 ml, 12 mmol) and the precipitate was collected by filtration to give **51** (1.38 g, 90% yield). An analytical sample was obtained by recrystallization from C_6H_6 as colorless crystals, mp 156—159 °C (lit.[37] mp 159—160 °C). NMR ($CDCl_3$) δ: 6.99 (1H, dd, $J=9$, 2 Hz), 7.03 (1H, s), 7.44 (1H, d, $J=9$ Hz). IR (KBr): 3148, 2241, 1600 cm^{-1}. MS *m/z*: 155 ($M^+ + 2$), 153 (M^+). *Anal.* Calcd for C_7H_4ClNO: C, 54.75; H, 2.63; N, 9.12. Found: C, 54.65; H, 2.48; N, 9.03.

Method B: Pellets of KOH (10.8 g, 0.193 mol) were added portionwise to a stirred solution of **48** (19.58 g, 75 mmol) obtained above in DMSO (40 ml) at 120—130 °C and stirring was continued for 10 min. After cooling, the solution was poured into ice-water and the whole was acidified with concentrated HCl. The resulting precipitate was collected by filtration, washed with H_2O and dried *in vacuo* to give **51** (10.09 g, 88% yield) as pale brown crystals, which were used for the next step without further purification. The NMR, IR and mass spectra were identical with those of the sample prepared by method A.

(*R*)-(−)-1-(5-Chloro-2-cyanophenoxy)-2,3-epoxypropane [(*R*)-3] Method A: Compound **51** (13.5 g, 88 mmol) was added portionwise to a stirred mixture of 60% NaH in oil (3.84 g, 96 mmol) and DMF (50 ml) with ice-cooling. The whole was stirred for 30 min at room temperature, then a solution of (*R*)-1-tosyloxy-2,3-propanediol acetonide [(*R*)-**52**] (25.7 g, 80 mmol) in DMF (30 ml) was added dropwise to it. This mixture was stirred for 5 h at 100 °C and poured into ice-water. The separated oily material was extracted with Et_2O. The organic layer was washed with H_2O, dried over $MgSO_4$ and evaporated under reduced pressure. Chromatography of the residue on a silica gel column with C_6H_6 gave (*S*)-**53** (20.08 g, 84% yield) as colorless crystals, mp 66—69 °C. NMR ($CDCl_3$) δ: 1.40 (3H, s), 1.46 (3H, s), 3.80—4.30 (4H, m), 4.30—4.70 (1H, m), 6.90—7.10 (2H, m), 7.49 (1H, d, $J=9$ Hz). MS *m/z*: 267 (M^+).

A mixture of (*S*)-**53** (3.71 g, 13.9 mmol), trifluoroacetic acid (0.4 ml) and MeOH (40 ml) was stirred overnight at room temperature and evaporated under reduced pressure. iso-Pr_2O was added to the residue and the precipitate was collected by filtration to give (*R*)-**54** (2.52 g, 80% yield) as colorless crystals. MS *m/z*: 227 (M^+).

A solution of *p*-TsCl (1.85 g, 9.71 mmol) in C_6H_6 (25 ml) was added dropwise to a solution of (*R*)-**54** (2.2 g, 9.67 mmol) in pyridine (6 ml) with ice-cooling. The reaction mixture was stirred overnight at room temperature, then diluted with C_6H_6. The whole was washed with 1 N HCl and H_2O, dried over $MgSO_4$ and evaporated under reduced pressure. Chromatography of the residue on a silica gel column with C_6H_6 gave (*S*)-**55** (2.73 g, 87% yield) as a colorless viscous oil. NMR ($CDCl_3$) δ: 1.63 (1H, br s), 2.42 (3H, s), 3.85—4.40 (5H, m), 6.94 (1H, d, $J=2$ Hz), 7.04 (1H, dd, $J=8$, 2 Hz), 7.33 (2H, d, $J=8$ Hz), 7.47 (1H, d, $J=8$ Hz), 7.80 (2H, d, $J=8$ Hz). MS *m/z*: 381 (M^+).

A 20% aqueous NaOH solution (1.36 ml) was added dropwise to a solution of (*S*)-**55** (1.36 g, 3.56 mmol) in DMSO (3 ml) with ice-cooling. The mixture was stirred for 1 h, then H_2O was added. The whole was extracted with AcOEt. The organic layer was washed three times with H_2O, dried over $MgSO_4$ and evaporated under reduced pressure. Chromatography of the residue on a silica gel column with C_6H_6 gave (*R*)-**3** (431 mg, 58% yield) as colorless needles, whose spectral data were identical with those of a sample obtained by method C. The retention times of the major and minor peaks on HPLC [mobile phase, *n*-hexane–iso-PrOH (95 : 5)] were 21.5 and 18.9 min, respectively, and the optical purity was 85% ee.

Method B: Compound **51** (368 mg, 2.4 mmol) obtained above was added portionwise to a stirred mixture of 60% NaH in oil (100 mg, 2.5 mmol) and DMF (10 ml) with ice-cooling. The reaction mixture was stirred for 30 min at room temperature, then (*R*)-glycidyl 3-nitrobenzenesulfonate [(*R*)-**56**] (518 mg, 2 mmol) was added. The whole was stirred for 22 h at room temperature. The resulting solution was evaporated under reduced pressure and ice-water was added to the residue. The whole was extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. Chromatography of the residue on a silica gel column with C_6H_6 gave (*R*)-**3** (358 mg, 85% yield) as colorless crystals, whose spectral data were identical with those of a sample obtained as described below. The optical purity was 93% ee on HPLC [the same conditions as above]. t_R 21.5 min.

Method C: A mixture of **51** (30.7 g, 0.2 mol) obtained above and (*S*)-epichlorohydrin [(*S*)-**57**] (25.9 g, 0.28 mol) was stirred for 2 h at 120 °C. After the mixture had cooled, the reaction mixture was dissolved in toluene (400 ml). Then a solution of NaOH (9.6 g, 0.24 mol) and benzyltriethylammonium chloride (2.28 g, 10 mmol) in H_2O (90 ml) was added dropwise with stirring at room temperature. Stirring was continued for 2 h, and the organic layer was separated, dried over $MgSO_4$ and evaporated under reduced pressure. Chromatography of the residue on a silica gel column with C_6H_6 gave crude (*R*)-**3** (35.76 g, 86% yield, 98% ee). Recrystallization from EtOH gave (*R*)-**3** (26.4 g, 66% yield) as colorless needles, mp 85—86 °C. NMR ($CDCl_3$) δ: 2.75—3.00 (2H, m), 3.25—3.50 (1H, m), 4.10 (1H, dd, $J=12.5$, 6 Hz), 4.36 (1H, dd, $J=12.5$, 3 Hz), 6.80—7.10 (2H, m), 7.45 (1H, d, $J=9$ Hz). IR (KBr): 2228 cm^{-1}. MS *m/z*: 209 (M^+). *Anal.* Calcd for $C_{10}H_8ClNO_2$: C, 57.29; H, 3.85; N, 6.68. Found: C, 57.34; H, 4.13; N, 6.56. $[\alpha]_D^{20}$ −9.93° ($c=1.00$, EtOH). The optical purity was 99.5% ee on HPLC [the same conditions as above]. t_R 21.5 min.

(*S*)-(+)-1-(5-Chloro-2-cyanophenoxy)-2,3-epoxypropane [(*S*)-3] In the same manner as described above, crude (*S*)-**3** (33.27 g, 79% yield, 95% ee) was prepared from **51** (30.7 g, 0.2 mol) obtained above and (*R*)-epichlorohydrin [(*R*)-**57**] (25.9 g, 0.28 mol). Recrystallization from EtOH gave (*S*)-**3** (24.75 g, 59% yield) as colorless needles, mp 85—86 °C. The NMR, IR and mass spectra of (*S*)-**3** were identical with those of (*R*)-**3**. *Anal.* Calcd for $C_{10}H_8ClNO_2$: C, 57.29; H, 3.85; N, 6.68. Found: C, 57.36; H, 4.13; N, 6.57. $[\alpha]_D^{20}$ +9.90° ($c=1.00$, EtOH). The optical purity was 100% ee on HPLC [the same conditions as above]. t_R 18.9 min.

(*R*)-(−)-1-(5-Chloro-2-cyanophenoxy)-3-chloro-2-propanol [(*R*)-58] Concentrated HCl (2 ml, 23.2 mmol) was added dropwise to a stirred solution of (*S*)-**3** (1.0 g, 4.8 mmol) obtained above in $CHCl_3$ (10 ml) with ice-cooling. Stirring was continued for 30 min, then the organic layer was separated, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was recrystallized from AcOEt to give (*R*)-**58** (1.05 g, 89% yield) as colorless prisms, mp 110—112 °C. NMR ($CDCl_3$) δ: 2.55 (1H, d, $J=6$ Hz), 3.81 (2H, d, $J=5$ Hz), 4.10—4.45 (3H, m), 7.01 (1H, s), 7.06 (1H, d, $J=9$ Hz), 7.51 (1H, d, $J=9$ Hz). IR (KBr): 2228 cm^{-1}. MS *m/z*: 247 ($M^+ + 2$), 245 (M^+), 153 (base peak). *Anal.* Calcd for $C_{10}H_9Cl_2NO_2$: C, 48.81; H, 3.69; N, 5.69. Found: C, 48.76; H, 3.68; N, 5.87. $[\alpha]_D^{27}$ −23.7° ($c=1.00$, EtOH).

(*S*)-(+)-1-(5-Chloro-2-cyanophenoxy)-3-chloro-2-propanol [(*S*)-58] In the same manner as described above, (*S*)-**58** (922 mg, 79% yield) was prepared from (*R*)-**3** (1.0 g, 4.8 mmol) obtained above. Recrystallization from AcOEt gave colorless prisms, mp 111—113 °C. The NMR, IR and mass spectra of (*S*)-**58** were identical with those of (*R*)-**58**. *Anal.* Calcd for $C_{10}H_9Cl_2NO_2$: C, 48.81; H, 3.69; N, 5.69. Found: C, 48.93; H, 3.66; N, 5.96. $[\alpha]_D^{27}$ +26.3° ($c=1.00$, EtOH).

(R_A,S_B)-(−)-6-[4-[2-[3-(5-Chloro2-cyanophenoxy)-2-hydroxypropylamino]-2-methylpropylamino]phenyl]-4,5-dihydro-5-methylpyridazin-3(2*H*)-one Monoethyl Maleate (Salt) (1c) A solution of (*R*)-**2** (3.0 g, 10.95 mmol) obtained above and (*S*)-**3** (2.52 g, 12.05 mmol) obtained above in *tert*-BuOH (90 ml) was stirred for 24 h at 60—65 °C and then evaporated under reduced pressure. Chromatography of the residue on a silica gel column with $CHCl_3$–MeOH (100 : 1) quantitatively gave the free base of **1c** (5.29 g) as a colorless viscous oil.

A solution of maleic acid monoethyl ester (1.57 g, 10.9 mmol) in EtOH (5 ml) was added to a solution of the free base of **1c** (5.29 g, 10.95 mmol) in EtOH (30 ml) with stirring. Stirring was continued overnight, and the resulting precipitate was collected by filtration. Recrystallization from acetone gave **1c** (5.16 g, 98% yield) as colorless needles, mp 141—143 °C. NMR (CD_3OD) δ: 1.16 (3H, d, $J=7$ Hz), 1.24 (3H, t, $J=7$ Hz), 1.44 (6H, s), 2.32 (1H, dd, $J=17$, 2 Hz), 2.70 (1H, dd, $J=17$, 7 Hz), 2.97—3.77 (3H, m), 3.43 (2H, s), 4.13 (2H, q, $J=7$ Hz), 4.13—4.50 (3H, m), 5.78 (1H, d, $J=12$ Hz), 6.50 (1H, d, $J=12$ Hz), 6.75 (2H, d, $J=9$ Hz), 7.12 (1H, dd, $J=8$, 2 Hz), 7.25 (1H, d, $J=2$ Hz), 7.49 (1H, d, $J=8$ Hz), 7.49 (2H, d, $J=9$ Hz). IR (KBr): 3404, 3218, 2218, 1715, 1682 cm^{-1}. MS *m/z*: 483 (M^+), 330, 267, 114 (base peak). *Anal.* Calcd for $C_{25}H_{30}ClN_5O_3$·

$C_6H_8O_4$: C, 59.27; H, 6.10; N, 11.15. Found: C, 59.27; H, 6.17; N, 11.03. $[\alpha]_D^{20}$ $-198.6°$ ($c=1.00$, EtOH). HPLC analysis was carried out under the following two conditions: 1) column, ULTRON ES-OVM (Shinwa Chemical Industry); mobile phase, 20 mM HCO_2NH_4–CH_3CN (1000 : 42); detector, UV absorption at 326 nm; 2) column, ULTRON ES-PEPSIN (Shinwa Chemical Industry); mobile phase, 20 mM HCO_2NH_4 (pH 5.0)–EtOH (5 : 1); detector, UV absorption at 326 nm. Compound **1c** showed a single peak at the retention time of 58.6 min under condition 1 and 99% at the retention time of 26.2 min under condition 2.

(S_A,S_B)-(+)-6-[4-[2-[3-(5-Chloro-2-cyanophenoxy)-2-hydroxypropylamino]-2-methylpropylamino]phenyl]-4,5-dihydro-5-methylpyridazin-3(2*H*)-one Monoethyl Maleate (Salt) (1a) In the same manner as described above, **1a** (570 mg, 64% yield) was obtained by the reaction of (*S*)-**2** (390 mg, 1.42 mmol) with (*S*)-**3** (315 mg, 1.5 mmol). Recrystallization from acetone gave colorless needles, mp 141—143 °C. The NMR, IR and mass spectra of **1a** were identical with those of **1c**. *Anal.* Calcd for $C_{25}H_{30}ClN_5O_3 \cdot C_6H_8O_4$: C, 59.27; H, 6.10; N, 11.15. Found: C, 59.46; H, 6.23; N, 11.31. $[\alpha]_D^{20}$ $+175.9°$ ($c=1.00$, EtOH). Compound **1a** showed a single peak at the retention time of 45.4 min under condition 1 and 99% at the retention time of 29.1 min under condition 2.

(S_A,R_B)-(+)-6-[4-[2-[3-(5-Chloro-2-cyanophenoxy)-2-hydroxypropylamino]-2-methylpropylamino]phenyl]-4,5-dihydro-5-methylpyridazin-3(2*H*)-one Monoethyl Maleate (Salt) (1b) In the same manner as described above, **1b** (739 mg, 72% yield) was obtained by the reaction of (*S*)-**2** (447 mg, 1.63 mmol) with (*R*)-**3** (361 mg, 1.72 mmol). Recrystallization from acetone gave colorless needles, mp 141—143 °C. The NMR, IR and mass spectra of **1b** were identical with those of **1c**. *Anal.* Calcd for $C_{25}H_{30}ClN_5O_3 \cdot C_6H_8O_4$: C, 59.27; H, 6.10; N, 11.15. Found: C, 59.40; H, 6.18; N, 11.24. $[\alpha]_D^{20}$ $+198.5°$ ($c=1.00$, EtOH). Compound **1b** showed a single peak at the retention time of 49.4 min under condition 1 and 99.5% at the retention time of 44.9 min under condition 2.

(R_A,R_B)-(−)-6-[4-[2-[3-(5-Chloro-2-cyanophenoxy)-2-hydroxypropylamino]-2-methylpropylamino]phenyl]-4,5-dihydro-5-methylpyridazin-3(2*H*)-one Monoethyl Maleate (Salt) (1d) In the same manner as described above, **1d** (747 mg, 65% yield) was obtained by the reaction of (*R*)-**2** (500 mg, 1.82 mmol) with (*R*)-**3** (404 mg, 1.93 mmol). Recrystallization from acetone gave colorless needles, mp 141—143 °C. The NMR, IR and mass spectra of **1d** were identical with those of **1c**. *Anal.* Calcd for $C_{25}H_{30}ClN_5O_3 \cdot C_6H_8O_4$: C, 59.27; H, 6.10; N, 11.15. Found: C, 59.49; H, 6.22; N, 11.21. $[\alpha]_D^{20}$ $-178.9°$ ($c=1.00$, EtOH). Compound **1d** showed a single peak at the retention time of 77.2 min under condition 1 and 99% at the retention time of 41.2 min under condition 2.

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