Asymmetric Reduction of a 1,5-Benzothiazepine Derivative with Sodium Borohydride−(*S*)-α-Amino Acids: An Efficient Synthesis of a Key Intermediate of Diltiazem

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Received May 22, 1996[⊗]

A key intermediate of diltiazem synthesis, (2*S*,3*S*)-2,3-dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one [(2*S*,3*S*)-**1**], has been efficiently synthesized by an asymmetric reduction of the prochiral ketone, 2-(4-methoxyphenyl)-1,5-benzothiazepine-3,4(2*H*,5*H*)-dione (**3**), with $NaBH_4$ and chiral α-amino acids. As the chiral sources, *β*-branched-chain amino acids, such as (*S*)-valine, (*S*)-isoleucine, and (*S*)-*tert*-leucine, were found to be effective. In particular, using (*S*)-*tert*-leucine as a ligand resulted in the formation of (2*S*,3*S*)-**1** with excellent enantioselectivity. (95% ee for *cis*-isomers). The addition of AcOH to the reaction permitted further improvement of both conversion and stereoselectivity. As a result, optically pure (2*S*,3*S*)-**1** could be isolated in 86% yield. This asymmetric reduction proceeded via dynamic kinetic resolution and made it possible to control the two adjacent asymmetric carbons through keto−enol tautomerism.

Introduction

Today diltiazem (**4**),[1] a representative calcium antagonist, is used throughout the world as a remedy for angina and hypertension. Diltiazem is a 1,5-benzothiazepine derivative and has two asymmetric carbon atoms at the C-2 and C-3 positions. Among the possible diastereomers, the (2*S*,3*S*)-isomer exhibits strong coronary vasodilating activity; therefore, stereoselective synthesis of the (2*S*,3*S*)-isomer has been attracting great attention.

Diltiazem has been prepared through chemical[2] or enzymatic[3] optical resolutions of its intermediates. Recently, enzymatic preparation[4] of an intermediate, (2*R*,3*S*)-3-(4-methoxyphenyl)glycidic acid methyl ester, has been utilized in industrial production as a more economical method. However, even these optical resolutions have an inevitable disadvantage in that the theoretical maximum yield of the desired isomer does not exceed 50%. Lately, asymmetric syntheses[5] have been extensively studied from the view point of their high efficiency. In these, biochemical asymmetric reduction of the prochiral ketone 2-(4-methoxyphenyl)-1,5-benzothiazepine-3,4-(2*H*,5*H*)-dione (**3**)[6] to (2*S*,3*S*)-2,3-dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one [(2*S*,3*S*)-**1**] was reported.[7] As for the chemical reduction of the ketone, Morimoto *et al*. also reported that reduction with $NaBH_4$ gave the *cis*-hydroxy benzothiazepine stereoselectively.[8]

Generally, $NaBH_4$ is used as a mild and selective reducing agent, and reducing reagents modified with chiral sources are very useful for the asymmetric reduction of ketones. For example, use of phase transfer catalysts,[9] protein,[10] amino acids,[11] monosaccharide derivatives,[12] and carboxylic acids[12f,13] as chiral sources have been reported in ketone reductions. This information

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[⊗] Abstract published in *Advance ACS Abstracts,* October 15, 1996.

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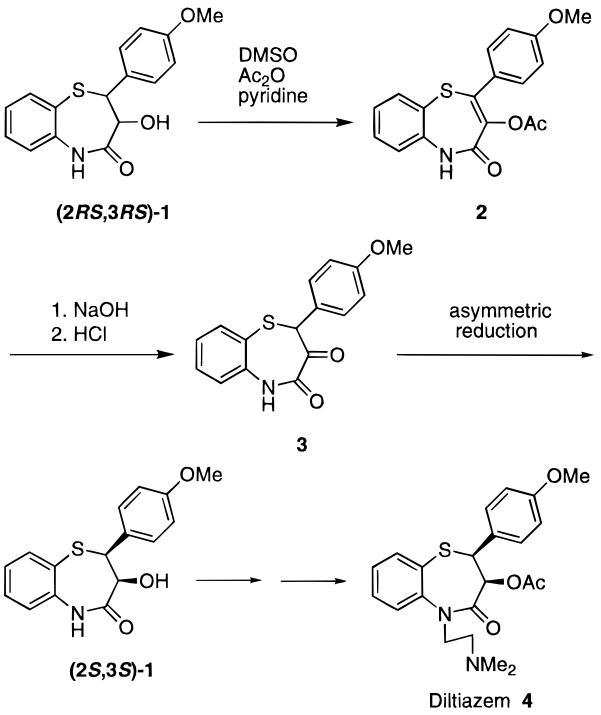
S0022-3263(96)00950-4 CCC: $12.00

Scheme 1



motivated us to study the asymmetric reduction of **3** with $NaBH_4$ and chiral sources. The present paper describes an efficient synthesis of a diltiazem intermediate via a highly enantioselective reduction with chirally modified $NaBH_4$ (Scheme 1).

Results

Search of Chiral Sources. The ketone **3** was prepared by oxidation[6,8] of the racemic alcohol (2*RS*,3*RS*)-**1**[14,15] followed by ester hydrolysis. With chiral reducing agents prepared from $NaBH_4$ and various α-amino acids, **3** was asymmetrically reduced to the corresponding stereoisomer of **1**.

As can be seen in Table 1, enantioselectivities were observed when α-amino acids possessing hydrocarbon side chains[16] were used. *Cis*-isomers predominated except for proline, and the use of (*S*)-amino acids gave the desired (2*S*,3*S*)-**1** as a major product.

We have also directed our attention to the relationship between the structure of the alkyl side chains and the selectivity of stereoisomers. That is, using (*S*)-alanine as a ligand gave little asymmetric induction (entry 2), whereas a substantial increase in the ratio of (2*S*,3*S*)-**1** was realized when longer straight or γ-branched-chain amino acids were employed (entries 3−6). Furthermore, β-branched-chain amino acids, (*S*)-valine, (*S*)-isoleucine, and (*S*)-*tert*-leucine, induced relatively high stereoselectivities (entries 7−9). In particular, (*S*)-*tert*-leucine exhibited an excellent result with a stereoselectivity of 89% in favor of (2*S*,3*S*)-**1** (95% ee for *cis*-isomers). Similarly, the reducing agent from (*R*)-*tert*-leucine provided (2*R*,3*R*)-**1** with an equally high ratio (entry 10). This successful result prompted us to examine the effect of aromatic side chain amino acids on stereoselectivities. Unfortunately, phenylalanine and phenylglycine were not as effective as we expected (entries 12 and 13).

From the above results, we have selected (*S*)-*tert*-leucine as a favorable chiral source for asymmetric reduction.

Effect of Additives. In order to obtain the desired (2*S*,3*S*)-**1** in higher yield, we investigated this reaction in more detail. Figure 1 shows the typical time course of the asymmetric reduction at 0 °C, and the following phenomena were found: (a) the reaction proceeded to a conversion of 60% immediately after the beginning and at this time the ratio of (2*S*,3*S*)-**1** was nearly 90%; (b) the rate of the reaction became slow and the ratio of (2*S*,3*S*)-**1** decreased with extended time; (c) the reaction was almost completed after 16 h, but the ratio of (2*S*,3*S*)-**1** dropped to only 76%. These results suggested us that, to obtain (2*S*,3*S*)-**1** in higher yield, the reaction must proceed with the high selectivity observed at the beginning of the reaction. Therefore, the effect of additives was examined to improve the selectivity.

Table 2 shows the results when 1 equiv of various additives was added to the reaction. As can be seen, MeOH and H_2O did not improve the selectivity. Triethylamine improved the selectivity, but the conversion was not high. Interestingly, AcOH exhibited a fairly good effect in both the conversion and the selectivity. Consequently, various addition methods of AcOH were examined in detail, as shown in Table 3. When 1 equiv of AcOH was added at the beginning of the reaction, the conversion was 86% and the selectivity of (2*S*,3*S*)-**1** was 76% (entry 1). However, in the case of AcOH addition after 0.5 h, the yield and selectivity increased to 95 and 82%, respectively (entry 2). Moreover, divided addition of 1 equiv of AcOH gave an apparent elevation of selectivity (entries 3−5). Under these conditions, the reactions were almost complete in 3 h with good stereoselectivity. Thus the divided addition of AcOH was found to be effective for the improvement of both conversion and stereoselectivity.

Effect of Temperature. In the final stage of our investigation, we evaluated the effect of the reaction temperature. Using the divided addition method with AcOH, the asymmetric reductions were carried out at various temperatures (Table 4). A characteristic tendency of the reaction was noticed. That is, at 20 °C the reduction was complete within 3 h but with only 80% (2*S*,3*S*)-**1** selectivity (entry 1). In contrast, as the reaction temperature was lowered, the selectivity increased and the rate of reaction became slow (entries 2−4). Accordingly, it seemed reasonable that the reaction should be performed at lower temperature with prolonged reaction time, so as to finish with a higher (2*S*,3*S*)-**1** ratio. Finally, we were able to achieve the reaction with 98% conversion and 91% (2*S*,3*S*)-**1** selectivity when it was carried out at −30 °C for 60 h with divided addition of AcOH (entry 5). Figure 2 shows the improved time course under these reaction conditions.

Isolation of (2*S*,3*S*)-1 and Recovery of (*S*)-*tert*-Leucine. Because we have found satisfactory conditions for the reaction, actual isolation of (2*S*,3*S*)-**1** was attempted. The reducing agent, $NaBH_4$−(*S*)-*tert*-leucine, was used at 1.5 equiv to the ketone **3**, and the reaction was conducted at −30 °C for 60 h with addition of AcOH. After removing the (*S*)-*tert*-leucine from the reaction mixture, the crude product was purified in 2-propanol to isolate optically pure (2*S*,3*S*)-**1** in 86% yield. Further-

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Table 1. Asymmetric Reduction of 3 with the Reagents Prepared from $NaBH_4$ and Optically Active α-Amino Acids[a]

entry	amino acid RCH(NH$_2$)COOH	structure of side chain R	conversion[b] (%)	ratio of stereoisomer **1**[b]			
				cis		*trans*	
				(2*S*,3*S*)[c]	(2*R*,3*R*)[c]	(2*R*,3*S*)[d]	(2*S*,3*R*)[d]
1[e]	none		90	46	46	4	4
2	(*S*)-alanine	CH_3	78	46	42	7	5
3	(*S*)-α-aminobutyric acid	CH_2CH_3	55	57	21	15	7
4	(*S*)-norvaline	$CH_2CH_2CH_3$	52	57	22	14	7
5	(*S*)-norleucine	$CH_2CH_2CH_2CH_3$	50	57	22	14	7
6	(*S*)-leucine	$CH_2CH(CH_3)_2$	58	58	21	14	7
7	(*S*)-valine	$CH(CH_3)_2$	64	74	10	13	3
8	(*S*)-isoleucine	$CH(CH_3)CH_2CH_3$	62	74	8	15	3
9	(*S*)-*tert*-leucine	$C(CH_3)_3$	65	**89**	2	8	1
10	(*R*)-*tert*-leucine	$C(CH_3)_3$	65	2	**89**	1	8
11	(*S*)-proline	$CH_2CH_2CH_2(N^{\alpha})$	52	29	1	69	1
12	(*S*)-phenylalanine	CH_2Ph	40	37	31	24	8
13	(*S*)-phenylglycine	Ph	48	61	19	15	5

[a] Conditions $NaBH_4$−amino acid (1.5 mmol), **3** (1 mmol), 0 °C, 1 h, THF. [b] Determined by HPLC analysis. [c] Authentic samples were prepared according to refs 2a and 2b. [d] Authentic samples were prepared by asymmetric reduction of **3** with $NaBH_4$−(*S*)- and (*R*)-proline system (See experimental Section for details). [e] Reduction was carried out with $NaBH_4$ alone.

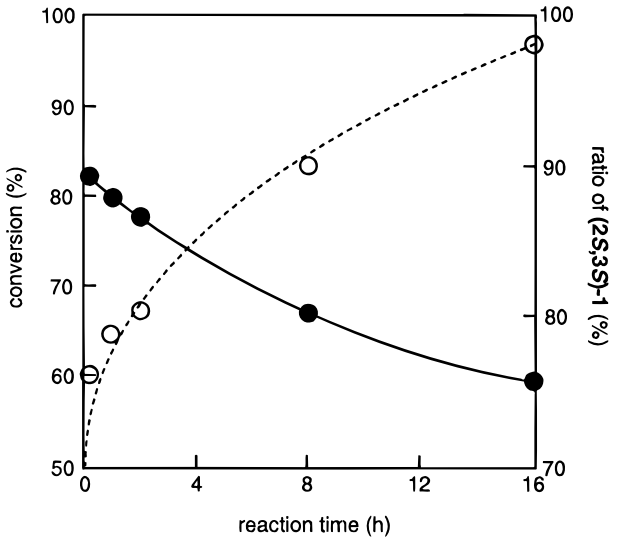

Figure 1. Time course of the asymmetric reduction of **3** with $NaBH_4$−(*S*)-*tert*-leucine at 0 °C. Conversion (dashed line); ratio of (2*S*,3*S*)-**1** (solid line).

Table 2. Effect of Additives on Asymmetric Reduction[a]

entry	additive	conversion[b] (%)	ratio of stereoisomer **1**[b]			
			cis		*trans*	
			(2*S*,3*S*)	(2*R*,3*R*)	(2*R*,3*S*)	(2*S*,3*R*)
1	none	97	76	16	6	2
2	MeOH	97	71	20	6	3
3	H_2O	98	73	19	6	2
4	Et_3N	80	82	11	7	1
5	AcOH	95	82	6	11	1

[a] Conditions: $NaBH_4$−(*S*)-*tert*-leucine (1.5 mmol), **3** (1 mmol), additive (1 mmol), 0 °C, 16 h, THF. [b] Determined by HPLC analysis.

more, efficient recovery of the chiral source (*S*)-*tert*-leucine is important for an economical synthetic method. (*S*)-*tert*-Leucine could be recovered almost quantitatively without racemization, and use of recycled material for the asymmetric reduction caused no problem.

Discussion

As described above, the yield of (2*S*,3*S*)-**1** was 86% in the asymmetric reduction. To obtain (2*S*,3*S*)-**1** in over 50% yield, it is necessary that the C-3 ketone is not only reduced asymmetrically, but that the configuration at the C-2 position is preferably controlled. Accordingly, this reaction satisfies the following two requirements: (1) the racemization between (2*S*)-**3** and (2*R*)-**3** is rapid; (2) the rate constant *k1* is much larger than *k2*. It can therefore be concluded that the desired (2*S*,3*S*)-**1** was produced selectively among the four possible stereoisomers via dynamic kinetic resolution[17] (Scheme 2).

The possible reasons for the improvement in the reaction by AcOH addition are as follows: (1) This reaction apparently proceeds via dynamic kinetic resolution with racemization at the C-2 position. AcOH may promote the racemization between (2*R*)-**3** and (2*S*)-**3**; (2) There was a possibility that the chiral reducing agent became deactivated during the reaction but might be reactivated by addition of AcOH.

In regard to the side-chain structures of α-amino acids as chiral sources, it is noteworthy that branches at the *β*-position exerted marked effects on providing high stereoselectivities. The steric bulkiness near the asymmetric carbon atom may play an important role in distinguishing not only the enantioface of the ketone but also the configuration at the C-2 position.

Up to now, attempts at isolating the reducing agent were unsuccessful. The structure of the reducing agent and the reaction mechanism remain to be examined.

Conclusions

We have discovered a new chiral reducing agent $NaBH_4$−(*S*)-*tert*-leucine which was very efficient in synthesizing a diltiazem intermediate. The asymmetric reduction proceeded via dynamic kinetic resolution and made it possible to control the configurations of the two adjacent asymmetric carbon atoms at the same time. This method may be one of the more promising routes to diltiazem developed to date.

Experimental Section

General Methods. Melting points are uncorrected. All of the solvents except THF and reagents were commercial products used without further purification. THF was distilled from sodium benzophenone ketyl before use. Analytical thin-layer chromatography (TLC) was performed on E. Merck precoated silica gel 60 F_{254} plates. Flash column chromatography was carried out on Merck silica gel 60 (230−400 mesh). Conversions from **3** to **1** were analyzed by reversed-phase HPLC. [Column: Waters Puresil 5 μm C18 120 Å 4.6 × 150

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Table 3. Effect of AcOH Addition on Asymmetric Reduction[a]

entry	additive, AcOH (equiv × times)	addition time (h)	reaction time (h)	conversion[b] (%)	ratio of stereoisomer **1**[b] *cis* (2*S*,3*S*)	*cis* (2*R*,3*R*)	*trans* (2*R*,3*S*)	*trans* (2*S*,3*R*)
1	1.0 × 1	0	20	86	76	7	15	2
2	1.0 × 1	0.5	16	95	82	6	11	1
3	0.5 × 2	0.5, 1.0	5	95	87	4	8	1
4	0.33 × 3	0.5, 1.0, 1.5	3	96	88	3	8	1
5	0.25 × 4	0.25, 0.5, 1.0, 1.5	3	96	88	3	8	1

[a] Conditions: $NaBH_4$−(*S*)-*tert*-leucine (1.5 mmol), **3** (1 mmol), 0 °C, THF. [b] Determined by HPLC analysis.

Table 4. Effect of Temperature on Asymmetric Reduction[a]

entry	reaction temperature (°C)	additive, AcOH (0.33 equiv × 3 times) addition time (h)	reaction time (h)	conversion[b] (%)	ratio of stereoisomer **1**[b] *cis* (2*S*,3*S*)	*cis* (2*R*,3*R*)	*trans* (2*R*,3*S*)	*trans* (2*S*,3*R*)
1	20	0.5, 1, 1.5	3	100	80	10	10	1
2	0	0.5, 1, 1.5	3	96	88	3	8	1
3	−15	0.5, 1, 1.5	3	89	90	2	7	1
4	−30	0.5, 1, 1.5	3	81	91	2	7	0
5	−30	1, 4, 20[c]	60	98	91	2	7	0

[a] Conditions: $NaBH_4$−(*S*)-*tert*-leucine (1.5 mmol), **3** (1 mmol), THF. [b] Determined by HPLC analysis. [c] AcOH (0.5 equiv) was added three times.

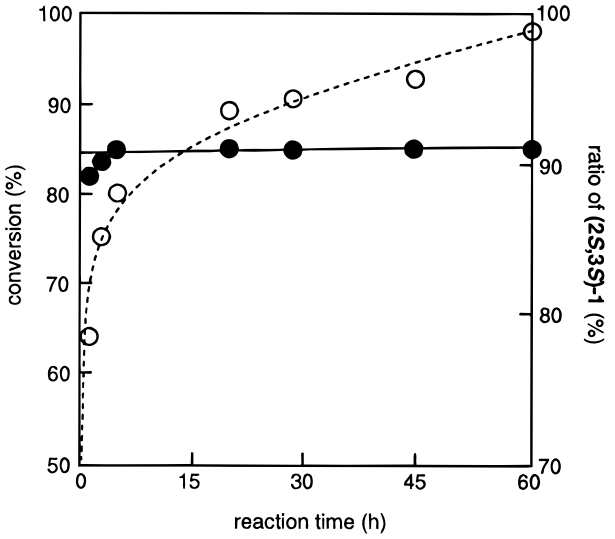


Figure 2. Time course of the asymmetric reduction of **3** with $NaBH_4$−(*S*)-*tert*-leucine at −30 °C with AcOH addition. Three portions of AcOH (0.5 equiv × 3) were added after 1, 4, and 20 h from the beginning of the reaction. Conversion (dashed line); ratio of (2*S*,3*S*)-**1** (solid line).

mm; Mobile Phase: CH_3CN/10 mM KH_2PO_4 (pH 3) = 50/50; flow rate: 0.5 mL/min; detection: UV 250 nm; temperature: 40 °C]. Four stereoisomers of **1** were analyzed by chiral HPLC. [Column: DAICEL CHIRALCEL OD 4.6 × 250 mm; mobile phase: *n*-hexane/EtOH = 85/15; flow rate: 0.5 mL/min; detection: UV 250 nm; temperature: 35 °C; t_R: (2*R*,3*R*) 22 min, (2*S*,3*S*) 28 min, (2*R*,3*S*) 32 min, (2*S*,3*R*) 35 min].

3-Acetoxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one (2). A modified literature procedure[8] was used to prepare **2**. *cis*-(2*RS*,3*RS*)-2,3-Dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one [(2*RS*,3*RS*)-**1**] (60.3 g, 0.2 mol) was dissolved in DMSO (156.3 g, 2.0 mol) and Ac_2O (51.1 g, 0.5 mol). A catalytic amount of pyridine (2.37 g, 0.03 mol) was added to the mixture. After the solution was stirred at rt for 24 h, H_2O (122 mL) was added over 10 min, and then further stirring was continued for 30 min. The crystalline material formed was collected by filtration, washed with MeOH, and dried to afford 57.44 g (84.1%) of the desired product **2**: mp 203−206 °C; IR (KBr, cm^{-1}) 1765, 1650, 1480; ^1H NMR (DMSO-d_6) δ. 2.04 (s, 3H), 3.79 (s, 3H), 6.97−7.68 (m, 8H), 10.82 (s, 1H); MS *m*/*z* 341 (M^+). Anal. Calcd for $C_{18}H_{15}NO_4S$: C 63.33; H 4.43; N 4.10. Found: C 63.07; H 4.56; N 4.00.

(2*RS*)-2-(4-Methoxyphenyl)-1,5-benzothiazepine-3,4-(2*H*,5*H*)-dione (3). A suspension of **2** (17.1 g, 0.05 mol) in MeOH (51 mL) was cooled in an ice bath, and then a solution of NaOH (5.0 g, 0.125 mol) in H_2O (63 mL) was added. The ice bath was removed, and the solution was allowed to stir at rt for 2 h. The reaction was neutralized by the addition of 2 N HCl (50 mL) and extracted with AcOEt. The organic phase was washed twice with H_2O, dried over $MgSO_4$, and concentrated to yield a viscous oil. The resulting oil was triturated in Et_2O to give 12.98 g (86.7%) of **3** as a yellow crystalline solid. The ^1H NMR spectrum of **3** in $CDCl_3$ revealed a mixture of keto and enol forms: mp 163−165 °C; IR (KBr, cm^{-1}) 1725, 1655, 1470; ^1H NMR ($CDCl_3$) δ. 3.80 and 3.83 (s, 3H), 5.45 (s, 1H), 6.64 (s, 1H), 6.86−7.78 (m, 8H), 8.95 and 9.00 (s, 1H); MS *m*/*z* 299 (M^+). Anal. Calcd for $C_{16}H_{13}NO_3S$: C 64.20; H 4.38; N 4.68. Found: C 64.31; H 4.36; N 4.53.

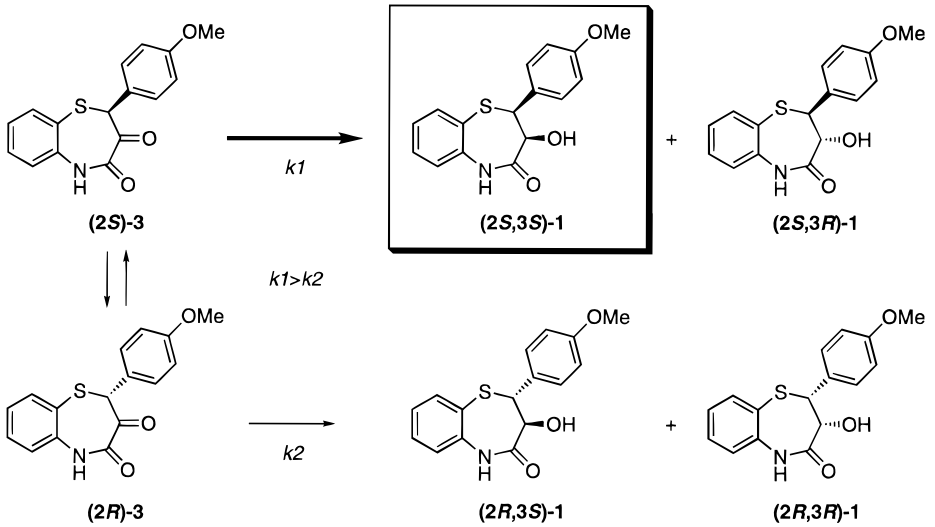
Preparation of the Authentic Samples [(2*S*,3*R*)-1 and (2*R*,3*S*)-1]. *trans*-(2*S*,3*R*)-2,3-Dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one [(2*S*,3*R*)-1]. A reducing agent was prepared by stirring the mixture of $NaBH_4$ (284 mg, 7.5 mmol) and (*R*)-proline (950 mg, 8.25 mmol) in THF (50 mL) at reflux temperature for 3 h under N_2. The reaction mixture was cooled to 0 °C, and then **3** (1497 mg, 5.0 mmol) was added. After stirring for 3 h at 0 °C, the reaction mixture was allowed to warm to rt. THF was evaporated *in vacuo*, and the yellow residue was triturated in H_2O (50 mL). The crystalline material formed was collected by filtration and washed with H_2O to give crude product, which was purified by flash chromatography using hexane and ethyl acetate (1:1−1:1.5) as eluent to yield (2*S*,3*R*)-**1** (590 mg, 39.2%). This was recrystallized from EtOH (20 mL) to give optically pure (2*S*,3*R*)-**1** (365 mg, 24.2%). The absolute configuration was determined to be (2*S*,3*R*) by X-ray crystallographic analysis: mp 196−198 °C; $[\alpha]^{20}_D$ = −837 (*c* 1.0, DMF); IR (KBr, cm^{-1}) 1690, 1515, 1475; ^1H NMR (DMSO-d_6) δ. 3.72 (s, 3H), 4.07 (dd, *J* = 10.2 Hz, 8.3 Hz, 1H), 4.35 (d, *J* = 10.2 Hz, 1H), 5.33 (d, *J* = 8.3 Hz, 1H), 6.83−7.56 (m, 8H), 10.21 (s, 1H); MS *m*/*z* 301 (M^+). Anal. Calcd for $C_{16}H_{15}NO_3S$: C 63.77; H 5.02; N 4.65. Found: C 63.81; H 4.85; N 4.42. The analytical data for this compound were in agreement with those reported by Tanaka *et al.*[18]

***trans*-(2*R*,3*S*)-2,3-Dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one [(2*R*,3*S*)-1].** (2*R*,3*S*)-**1** was prepared similarly using (*S*)-proline instead of (*R*)-proline.

General Procedure for Asymmetric Reduction of 3 with the Reagents Prepared from $NaBH_4$ and Optically

(18) Tanaka, T.; Inoue, H.; Date, T.; Okamura, K.; Aoe, K.; Takeda, M.; Kugita, H.; Murata, S.; Yamaguchi, T.; Kikkawa, K.; Nakajima, S.; Nagao, T. *Chem. Pharm. Bull.* **1992**, *40*, 1476.

Scheme 2



Active α-Amino Acids (Table 1). A reducing agent was prepared by stirring the mixture of $NaBH_4$ (57 mg, 1.5 mmol) and optically active α-amino acid (1.65 mmol) in THF (15 mL) at 60−65 °C for 3 h under N_2 (hydrogen evolution). The reaction mixture was cooled to 0 °C, and then **3** (299 mg, 1 mmol) was added. After stirring for 1 h, the conversion and the ratio of the four stereoisomers of **1** were analyzed by HPLC.

Time Course of the Asymmetric Reduction of 3 with $NaBH_4$−(*S*)-*tert*-Leucine (Figure 1). A reducing agent was prepared by stirring the mixture of $NaBH_4$ (57 mg, 1.5 mmol) and (*S*)-*tert*-leucine (216 mg, 1.65 mmol) in THF (15 mL) at 60−65 °C for 3 h under N_2. The reaction mixture was cooled to 0 °C, and then **3** (299 mg, 1.0 mmol) was added. After stirring for 10 min, 1 h, 2 h, 8 h, and 16 h, the conversions and ratios of (2*S*,3*S*)-**1** were analyzed by HPLC.

General Procedure for Asymmetric Reduction of 3 with $NaBH_4$−(*S*)-*tert*-Leucine in the Presence of an Additive (Table 2). The preparation of the chiral reducing agent, $NaBH_4$−(*S*)-*tert*-leucine, was similar to that described above. The reaction mixture was cooled to 0 °C and then **3** (299 mg, 1.0 mmol) was added. After stirring for 0.5 h, the additive (1.0 mmol) was added and then further stirring was continued for 15.5 h at 0 °C. Then conversion and ratio of four stereoisomers of **1** were analyzed by HPLC.

General Procedure for Asymmetric Reduction of 3 with $NaBH_4$−(*S*)-*tert*-Leucine under Various AcOH Addition Conditions (Table 3). The preparation of the chiral reducing agent, $NaBH_4$−(*S*)-*tert*-leucine, was similar to that described above. The reaction mixture was cooled to 0 °C, and then **3** (299 mg, 1.0 mmol) was added. The mixture was stirred at 0 °C with addition of AcOH. Then the conversion and the ratio of the four stereoisomers of **1** were analyzed by HPLC.

General Procedure for Asymmetric Reduction of 3 with $NaBH_4$−(*S*)-*tert*-Leucine at Various Reaction Temperatures (Table 4). The preparation of the chiral reducing agent, $NaBH_4$−(*S*)-*tert*-leucine, was similar to that described above. The reaction mixture was adjusted to a fixed temperature, and then **3** (299 mg, 1.0 mmol) was added. The mixture was stirred at the same temperature with addition of AcOH. Then the conversion and the ratio of the four stereoisomers of **1** were analyzed by HPLC.

Time Course of the Asymmetric Reduction of 3 with $NaBH_4$−(*S*)-*tert*-Leucine with AcOH Addition (Figure 2). The preparation of the chiral reducing agent, $NaBH_4$−(*S*)-*tert*-leucine, was similar to that described above. The reaction mixture was cooled to −30 °C, **3** (299 mg, 1.0 mmol) was added, and the mixture was stirred for 60 h at −30 °C. In the course of the reaction, three portions of AcOH (30 mg×3) were added after 1, 4, and 20 h from the beginning of the reaction (total 90 mg, 1.5 mmol). Conversions and ratios of (2*S*,3*S*)-**1** were analyzed by HPLC after 10 min, 1 h, 4 h, 19 h, 28 h, 44 h, and 60 h.

Isolation of (2*S*,3*S*)-1. *cis*-(2*S*,3*S*)-2,3-Dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one [(2*S*,3*S*)-1]. A reducing agent was prepared by stirring the mixture of $NaBH_4$ (189 mg, 5.0 mmol) and (*S*)-*tert*-leucine (722 mg, 5.5 mmol) in THF (50 mL) at 60−65 °C for 3 h under N_2. (If a lump of $NaBH_4$ remained unreacted, it was crushed with a spatula and reacted for an additional time). The reaction mixture was cooled to −30 °C, **3** (997 mg, 3.33 mmol) was added, and the mixture was stirred for 60 h at −30 °C. In the course of the reaction, three portions of AcOH (100 mg×3) were added after 1, 17, and 45 h (total 300 mg, 5.0 mmol). The reaction was allowed to warm to rt, THF was evaporated *in vacuo*, and the pale yellow residue was triturated in H_2O (50 mL). The crystalline material formed was collected by filtration and washed with H_2O to give the crude product (969 mg, 96.6%). This material consisted of a 93:7 mixture of *cis:trans* isomers, and the optical purity of the *cis*-isomers was 95% ee according to HPLC analysis. The crude product was refluxed for 3 h in 2-propanol (12 mL), cooled to 5 °C, and filtered to give optically pure (2*S*,3*S*)-**1** (867 mg, 86.4%): mp 200−202 °C; $[\alpha]^{22}_D = +115.6$ (*c* 0.5, DMF); IR (KBr, cm^{-1}) 1680, 1510, 1475; ^1H NMR (DMSO-d_6) δ. 3.76 (s, 3H), 4.29 (dd, J = 6.4 Hz, 6.6 Hz, 1H), 4.74 (d, J = 6.4 Hz, 1H), 5.05 (d, J = 6.6 Hz, 1H), 6.87−7.62 (m, 8H), 10.31 (s, 1H); MS *m*/*z* 301(M^+). Anal. Calcd for $C_{16}H_{15}NO_3S$: C 63.77; H 5.02; N 4.65. Found: C 63.59; H 5.07; N 4.55.

Recovery of (*S*)-*tert*-Leucine. To the mother liquor, which was obtained after the isolation of the crude (2*S*,3*S*)-**1** described above, was added 6 N HCl (20 mL), and then the solution was stirred for 1.5 h at 70 °C. After cooling to rt, the solution was washed with $CHCl_3$ (20 mL) to remove organic contaminants. The aqueous layer was concentrated *in vacuo*, and again the residue was dissolved in H_2O (40 mL), and treated with cation-exchange resin (SK-1B, 20 mL). The resin was washed with H_2O (80 mL), and the amino acid was eluted with 5% NH_4OH (80 mL). The eluent was evaporated *in vacuo* to recover 712 mg (98.6%) of (*S*)-*tert*-leucine: $[\alpha]^{25}_D = +31.2$ (*c* 1.0, AcOH) [lit.[19] $[\alpha]^{25}_D = +30.0$ (*c* 1.0, AcOH)]

Acknowledgment. The authors thank the staff of the Analytical Department for elemental analyses and spectral measurements. We are also grateful to Dr. T. Tosa, R&D Executive of this company, and to Dr. M. Ikezaki, Director of this laboratory, for their encouragement.

JO960950W

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