

On the Stereoselectivity of Asymmetric Strecker Synthesis in a Cyclohexane System: Synthesis of Optically Active *cis*- and *trans*-1-Amino-2-hydroxycyclohexane-1-carboxylic Acids

Tetsuro Shinada,* Tadashi Kawakami, Hiroshi Sakai, Hiromi Matsuda, Taiki Umezawa, Masaki Kawasaki, Kosuke Namba, and Yasufumi Ohfune*

Graduate School of Science, Osaka City University, 3-3-138 Sugimoto, Sumiyoshi-ku, Osaka 558-8585

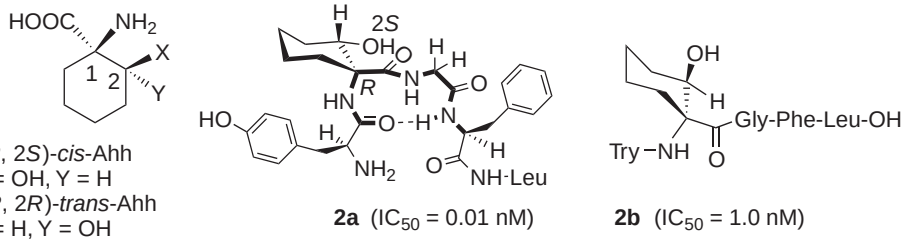
Received November 1, 2005; E-mail: Ohfune@sci.osaka-cu.ac.jp

Stereoselective synthesis of both optically active *cis*- and *trans*-1-amino-2-hydroxycyclohexane-1-carboxylic acids (Ahhs) **1a** and **1b** was accomplished by an asymmetric version of the Strecker synthesis. Stereochemical aspects of their chiral induction processes are investigated.

Functionalization of the hydroxy group of serine or threonine in peptides and proteins is an important biological process. For instance, their phosphorylation and glycosidation are associated with cell differentiation and signal transduction.[1] Furthermore, the hydroxy moiety plays a key role as a catalytic site in a class of serine proteases.[2] The above reactions are catalyzed by an enzyme and performed in a spatially limited enzyme pocket. In this circumstance, the conformation around the hydroxy group is fixed to facilitate these chemical modifications. Therefore, exploitation of the conformational demand of serine or threonine is an important subject not only for the elucidation of the enzyme reaction mechanisms at the molecular level, but also for the rational design of effective ligands.[3] In this context, we have synthesized *cis*- and *trans*-1-amino-2-hydroxycyclohexane-1-carboxylic acid (*cis*-Ahh **1a** and *trans*-Ahh **1b**), which can be viewed as conformational variants of serine or threonine.[4] Their effect on the peptide conformation and biological activity has been well documented by our recent studies,[5] i.e., incorporation of Ahh isomers into the Gly(2) residue of leucine–enkephalin (Leu–Enk) revealed that (1) each Ahh isomer restricted the local conformation of Leu–Enk to a β-turn conformation and (2) the *cis*-Ahh isomer **2a**, whose hydroxy group is fixed to an equatorial orientation, exhibited 17 times more potent binding activity to δ-opioid receptors of cultured rat brain membrane than that of Leu–Enk, while the potency of its *trans*-isomer **2b** having an axial orientation of the hydroxy group in the peptide was 1/100 of that of **2a** (Scheme 1).

The Ahh isomers **1** have been prepared from the 2-acyloxycyclohexanone **3a** possessing L-Phe as the acyloxy group using an asymmetric version of the Strecker synthesis.[4,6] The efficiency of this method has been demonstrated by the synthesis of a number of acyclic β-hydroxy-α,α-disubstituted α-amino acids and natural products in view of its high enantio- and diastereoselectivity, short-step conversion, and overall yields.[6] On the other hand, the synthesis of Ahh isomers involves the cyanide addition to a fused-bicyclic ketimine intermediate. This transformation was performed by the use of NaCN in 2-PrOH from **3a** without isolation of the ketimines **4a** and **5a** to give a mixture of the *cis*- and *trans*-α-amino nitriles **7a** and **8a** in 85% yield with moderate diastereoselectivity (*cis*/*trans* = 2–4:1). The major isomer was isolated by recrystallization and was converted to the *cis*-Ahh **1a**. The minor *trans*-isomer **1b** was obtained by chromatographic separation after conversion of the mixture to the corresponding α-imino nitriles **9a** and **10a**, followed by its hydrolysis[4] (Scheme 2).

However, in the previous synthesis, the stereochemical outcome of the cyanide addition to the ketimine intermediate of the cyclohexane system was not investigated in detail and supply of the *trans*-isomer **1b** was required. In this report, we wish to describe our extensive studies regarding (1) the effect of the chirality transferring groups employing L-Phe-, L-Trp-, L-Leu-, and L-*t*-Leu esters **3a**–**3d** on the ratio of both the ketimines (**4** vs **5**) and the α-amino nitriles (**7** vs **8**), (2) stereoselective synthesis of **1b**, (3) equilibrium experiments between **4** and **5**, and (4) conformational analysis of **4** and **5**.



1a (1*R*, 2*S*)-*cis*-Ahh X = OH, Y = H
1b (1*R*, 2*R*)-*trans*-Ahh X = H, Y = OH

2a (IC_{50} = 0.01 nM) **2b** (IC_{50} = 1.0 nM)

Scheme 1.

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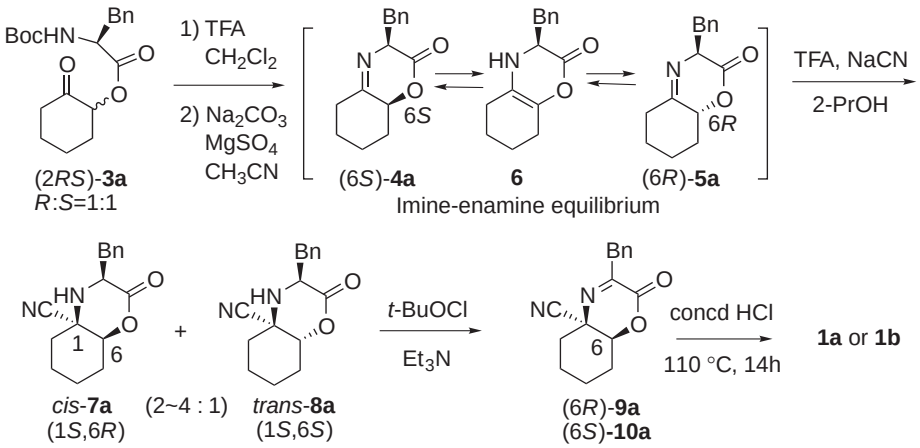
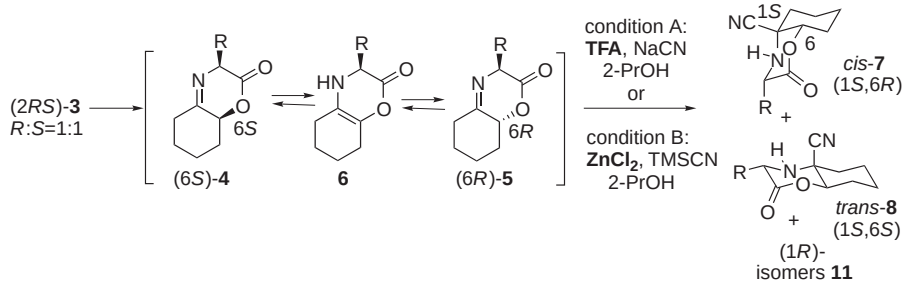
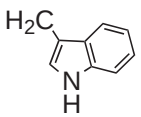


Scheme 2.

Table 1. Formation of α-Amino Nitriles **7**, **8**, and **11** from α-Amino Acid Esters **3**



	Substrate **3a**–**3d** R	Ratio of ketimines **4**:**5**	Yields and ratios of **7**:**8**:**11** [Yield/%]	
			Condition A (**TFA**)	Condition B ($\mathbf{ZnCl_2}$)
a	Bn (Phe)	50:50	66:34:N.D. [96][a)]	41:59:N.D. [89][a)]
b	 (Trp)	50:50	77:23:N.D. [56][a)]	33:67:N.D. [48][a)]
c	CH_2i-Pr (Leu)	50:50	39:42:19 [86]	18:71:11 [73]
d	*t*-Bu (*t*-Leu)	20:80	16:82:2 [88]	5:90:5 [80]

a) (1*R*)-**11a** and -**11b** were not detected (N.D.) by ^{1}H NMR.

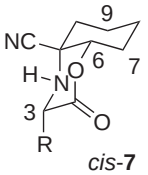
Results and Discussion

Effects of the Chirality Transferring Group and Stereoselective Synthesis of *trans*-Ahh (1b). Upon the asymmetric Strecker process for Ahh using L-Phe as the chirality transferring group, we initially presumed that the ketimine intermediates were under a rapid equilibrium between (6*S*)-**4a** and (6*R*)-**5a** via the enamine **6a**, where its composition would reflect the ratio of the resulting α-amino nitriles **7a** and **8a**. In this study, the intermediary ketimines were isolated and the ratios of the mixture of (6*S*)-**4** and (6*R*)-**5** were analyzed by their ^{1}H NMR data. The cyanide addition was performed using two reaction conditions: conditions A (NaCN, TFA) and B (TMSCN, $ZnCl_2$).[7] These results are depicted in Table 1 and are summarized by the following points: (1) ^{1}H NMR analysis of the isolated ketimines revealed that they consist of a 1:1 mixture of the (6*S*)- and (6*R*)-isomers **4** and **5**, indicating that each ketimine ratio is not in accord with that of the α-amino nitriles (*cis*-**7**/*trans*-**8**), except for the case of the ketimine derived from the Boc-*t*-Leu ester **3d**; (2) the Boc-L-Phe and Boc-L-Trp esters **3a** and **3b** bearing an aromatic ring afforded the *cis*-α-amino nitriles **7a** and **7b** as the major products under condition A; (3) preferential formation of the *trans*-α-amino nitriles **8a**–**8d** was observed under condition B. Among them, the *t*-Leu ester **3d** gave the highest *trans*-selectivity (*trans*-**8d**/*cis*-**7d** = 18:1); and (4) the cyanide addition to the ketimines having an alkyl side chain gave a small amount of the (1*R*)-isomers **11c** and **11d**, while such isomers were not produced at all upon cyanide addition to the ketimines possessing an aromatic group derived from **3a** and **3b**.

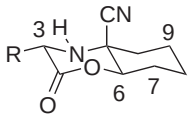
The structures of the α-amino nitriles **7b** and **7c** and **8b** and **8c** were assigned as depicted in Table 1 by comparison of their ^{1}H NMR data with those of **7a** and **7d** and **8a** and **8d** (vide infra). The C3 proton of all of the *cis*-adducts **7** was observed at a higher magnetic field than that of *trans*-**8**, and the C6 proton appeared in an opposite relationship (Table 2).

Upon oxidation of *cis*-**7a** to the corresponding α-imino nitrile **9a**, the use of DABCO/*t*-BuOCl (method A) was found

Table 2. Selected ^{1}H NMR Data of α-Amino Nitriles **7** and **8**[a)]



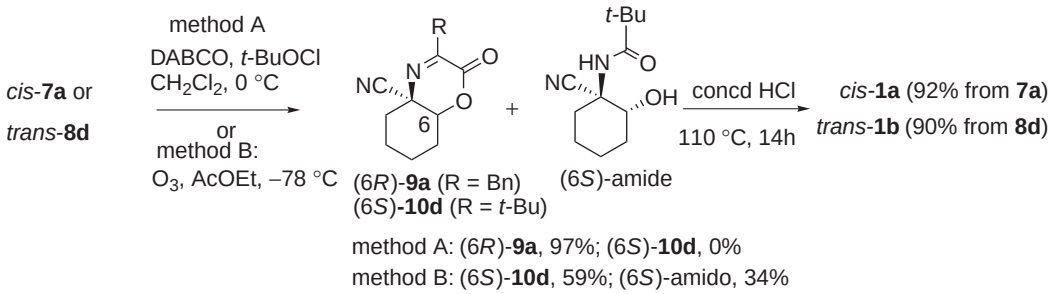
cis-**7**



trans-**8**

α-Amino nitriles	3-H	6-H	7-H*ax*	9-H*ax*
Phe-**7a**	4.14 [ddd, 8.8, 4.9, 3.7]	4.34 [ddd, 10.7, 4.8, 2.1]	1.4–1.6 [m]	1.2–1.4 [m]
Phe-**8a**	4.22 [dt, 9.8, 3.9]	3.96 [dd, 12.3, 4.3]	1.4–1.6 [m]	1.2–1.4 [m]
Trp-**7b**	4.18 [dt, 8.7, 3.6]	4.33 [dd, 10.2, 4.3]	1.4–1.6 [m]	1.2–1.4 [m]
Trp-**8b**	4.31 [dd, 9.6, 3.0]	3.98 [dd, 12.2, 4.1]	1.4–1.6 [m]	1.2–1.4 [m]
Leu-**7c**	3.89 [dd, 8.8, 4.2]	4.47 [dd, 8.8, 4.4]	1.5–1.7 [m]	1.3–1.5 [m]
Leu-**8c**	4.06 [dd, 8.4, 4.0]	4.10 [dd, 12.2, 4.1]	1.6–1.8 [m]	1.3–1.5 [m]
t-Leu-**7d**	3.62 [s]	4.38 [dd, 10.0, 4.9]	1.5–1.7 [m]	1.3–1.5 [m]
t-Leu-**8d**	3.75 [s]	4.07 [dd, 12.2, 4.4]	1.5–1.7 [m]	1.3–1.5 [m]

a) Chemical shifts and coupling constants are shown in δ (ppm) and J (Hz), respectively.

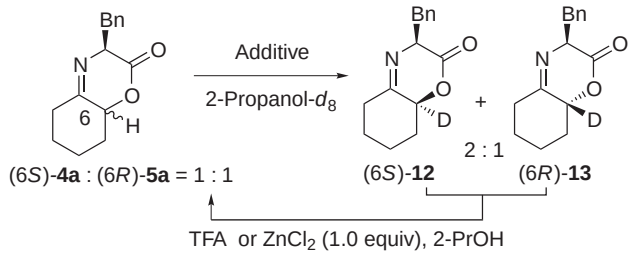


Scheme 3.

to be superior to the previous Et_3N/*t*-BuOCl oxidation (60–90% yield)[4,6] in view of its shortened reaction period (2 h) and high and reproducible yield (97–100%).[8] In particular, the *cis*-Ahh **1a** was obtained in 92% yield from **7a**. On the other hand, *trans*-**8d** having a sterically bulky *t*-Bu group was resistant to the method A resulting in complete recovery of **8d**. This problem was overcome by the use of O_3 oxidation (method B)[9] to give a mixture of **10d** and α-amido nitrile in excellent yield. Hydrolysis of the mixture afforded the optically pure (1*R*,2*R*)-*trans*-Ahh **1b** in 90% yield from **8d**. Thus, the structure of *trans*-**8d** was unambiguously confirmed and the stereoselective synthesis of the *trans*-Ahh **1b** was accomplished by means of L-*t*-Leu as the chiral auxiliary (Scheme 3).

Imine–Enamine Equilibrium and Conformational Analysis of Ketimines (6*S*)-4 and (6*R*)-5. We examined equilibrium experiments of the ketimines **4a** and **5a** using 2-propanol-d_8 in the presence or absence of the cyanide source (Table 3). Treatment of a 1:1 mixture of **4a** and **5a** with TFA in 2-propanol-d_8 reached equilibrium within 7 min to give a 2:1 mixture of mono deuterated (6*S*)-**12** and (6*R*)-**13**. The deuterium incorporation was also effected by $ZnCl_2$ within 2 h to give **12** and **13** in the same product ratio (2:1). On the other hand, the incorporation proceeded very slowly in the absence of additives. No incorporation was observed in the presence of NaCN without TFA or $ZnCl_2$. Treatment of a 2:1 mixture of deuterated **12** and **13** with TFA in 2-PrOH afforded a 1:1 mixture of **4a** and **5a**. These results clearly indicated the existence of the equilibrium between **4a** and **5a** via the enamine **6a** in 2-PrOH. The equilibrium experiments in 2-PrOH using Phe-, Leu-, and *t*-Leu ketimines **4a**, **4c**, and **4d** and **5a**, **5c**, and **5d** are summarized in Table 4. The initial ratios of the ketimines **4a** and **4d** and **5a** and **5d** were retained or slightly changed by treatment with TFA or $ZnCl_2$. In the case of a 1:1 mixture of **4c** and **5c**, the use of TFA did not affect the original ratio, but

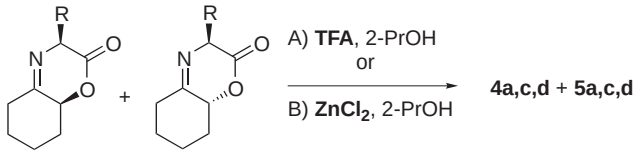
Table 3. Equilibrium Experiments of **4a** and **5a** in 2-Propanol-d_8[a)]



Additive	Time	Ratio **12**:**13**	*d*-Incorporation at C-6/%
None	72 h	2:1	100
CF_3CO_2D (1.0 equiv)	<7 min	2:1	100
$ZnCl_2$ (1.0 equiv)	2 h	2:1	100
NaCN (1.0 equiv)	72 h	—	0

a) All experiments were carried out at room temperature. A 1:1 mixture of **4a** and **5a** was used.

Table 4. Equilibrium Experiments of **4a**, **4c**, and **4d** and **5a**, **5c**, and **5d** in 2-PrOH



(6*S*)-**4a,c,d** (6*R*)-**5a,c,d**

Substrate	R	Initial ratio **4**:**5**	Ratio after equilibrium (**4**:**5**)[a]	
			A (**TFA**)	B ($\mathbf{ZnCl_2}$)
4a + **5a** (Phe)	Bn	50:50	50:50	50:50
4c + **5c** (Leu)	CH_2i-Pr	50:50	50:50	29:71
4d + **4d** (*t*-Leu)	*t*-Bu	21:79	17:83	13:87

a) Reactions were carried out at room temperature for 7 min under the condition A and for 2 h under the condition B.

$ZnCl_2$ gave *trans*-**5c** as the major isomer (**4c**/**5c** = 29:71).

With the above results in hand, we next inspected the ^{1}H NMR data of the ketimines **4** and **5** based on coupling constants and NOESY experiments (Table 5). In all cases, signals corresponding to the enamine **6** were not observed. Large *J* values (10–12 Hz) between 6-H and 7-H*ax* were observed in all (6*S*)- and (6*R*)-ketimines **4** and **5**, indicating that these protons are in an antiperiplanar relationship. In comparison of the homoallylic coupling constants ($^4J_{3\text{-H}-6\text{-H}}$) of the ketimines **4** and **5** with those reported of **14**,[10] the ketimine having a smaller $^4J_{\text{H-H}}$ value (≈1.8 Hz) was assigned to (6*R*)-**5**, whereas the larger *J* value (>3.1 Hz) was assigned to (6*S*)-**4**. These *J* values together with NOESY experiments suggested that the ketimines **4** and **5** possess a boat-like conformation[10] with the amino acid side chain oriented to a pseudoaxial position as shown in Fig. 1. In the case of the ketimines having an aromatic side chain, an unusual high field shift of 6-H for **5a** and **5b**, 7-H*ax* for **4a** and **4b**, and 9-H*ax* for **4b** was observed probably due to anisotropic effects by the aromatic group. In addition, the *J* values between the benzyl methylene group and 3-H ($J_{3\text{-}1'\text{H}}$ = 4.5, 4.5 Hz) suggested the local conformation to have a bisect form. These observations led **4a** and **4b** and **5a** and **5b** to have a stacking conformation where the α-face is completely shielded (Fig. 1). In contrast to **4a** and **4b**, none of the protons that shift to a higher magnetic field were observed in the case of the ketimines **4c** and **4d** and **5c** and **5d** derived from Leu and *t*-Leu. The dihedral angle between 2-H and 1′-Hs ($J_{3\text{-}1'\text{H}}$ = 5.7, 11.0 Hz) according to the Karplus equation indicated that the alkyl side chain of the Leu–ketimines **4c** and **5c** is exposed from the ketimine ring (Fig. 1).

Proposed Mechanism. From the above experiments, it is clearly understood that the facial selectivity (1*R* vs 1*S*) and the *cis*/*trans* selectivity upon cyanide addition to the ketimines are affected by the nature of the chirality transferring amino acids (aromatic vs alkyl side chain) and the reaction conditions (conditions A vs B). Regarding the diastereofacial selectivity, we propose that the exclusive formation of the (1*S*)-α-amino nitrile isomers **7a** and **7b** and **8a** and **8b** from Phe-**3a** and Trp-**3b** is attributed to the conformation of their ketimine intermediates, **4a** and **4b** and **5a** and **5b**, where the aromatic group of the ketimine intermediate shields the α-face from the attack of the cyanide ion. A small amount of the (1*R*)-isomers **11c** (conditions A: 1*S*/1*R* = 81:19 and B: 89:11) and **11d** (A: 98:2 and B: 95:5) obtained from **3c** and **3d** suggests that the α-face of their ketimine intermediates, **4c** and **4d** and **5c** and **5d**, is not sufficiently shielded due to the exo orientation of the alkyl group (Fig. 1). Regarding the *cis*/*trans* selectivity, additional experiments were performed to see whether an equilibrium exists between the α-amino nitriles **7a** and **8a** through the ketimines **4a** and **5a**. This has been often observed in a monocyclic α-amino nitrile system.[4,6] However, the presence of such an equilibrium in this case was ruled out by the fact that treatment of the α-amino nitriles **7a** and **8a** with $Na^{13}CN$/TFA in 2-PrOH and $Na^{12}CN$/TFA-d_1 in 2-PrOH-d_8 incorporated none of the ^{13}CN or D into **7a** and **8a**, respectively (Scheme 4). These results suggest that the cyanide addition to the ketimine is a rate-determining step under condition A since the equilibrium between the ketimines **4a** and **5a** reached a plateau within 7 min and the overall reaction takes 3 h. Therefore, the unusual stacking conformation of the ketimines derived from Phe-**3a** and Trp-**3b** would sterically hinder an axial attack of the cyanide ion to **5a** and **5b** to give *cis*-**7a** and -**7b** as the major product, respectively (Scheme 3). On the other hand, the *cis*/*trans* ratios of **7c**/**8c** and **7d**/**8d** having an alkyl side chain were almost in accord with those of their ketimines **4c**/**5c** and **4d**/**5d**, respectively. In these cases, the equilibrium between ketimines was also fast (Table 4). Significant differences of their conformation from **7a** and **7b** and **8a** and **8b** as well as stereoelectronic preference (axial attack)[11] for the cyanide addition might reflect the product ratios.

Regarding the *trans*-selectivity observed under condition B, $ZnCl_2$ plays an important role. In particular, the (6*R*)-ketimines **5c** and **5d** were preferentially formed under the equilibrium conditions using $ZnCl_2$ (Table 4). The ratios of the ketimines and the resultant α-amino nitriles were almost equal. As shown in Scheme 5, $ZnCl_2$ would contribute to stabiliza-

Table 5. Selected ^{1}H NMR Data of Ketimines **4** and **5**[a]

Ketimines	3-H	6-H	7-H*ax*	9-H*ax*
Phe-**4a**	4.57 [ddt, 4.6, 4.3, 3.2]	4.57 [ddd, 12.3, 5.9, 3.2]	**−0.02** [qd, 12.3, 3.9]	1.2–1.4 [m]
Phe-**5a**	4.74 [tt, 4.5, 1.8]	**3.26** [ddd, 12.3, 6.3, 1.8]	1.2–1.4 [m]	1.2–1.4 [m]
Trp-**4b**	4.61 [tt, 4.3, 3.5]	4.47 [ddd, 12.3, 5.7, 3.5]	**−0.21** [qd, 12.3, 4.0]	**0.23** [qt, 13.5, 4.2]
Trp-**5b**	4.77 [ddt, 4.3, 4.1, 1.5]	**3.24** [ddd, 12.1, 6.4, 1.5]	1.2–1.4 [m]	1.2–1.4 [m]
Leu-**4c**	4.01 [ddt, 11.0, 5.7, 3.5]	4.77 [ddd, 12.9, 6.9, 3.5]	1.4–1.7 [m]	1.4–1.7 [m]
Leu-**5c**	4.30 [ddt, 7.8, 6.3, 1.5]	4.80 [ddd, 11.0, 7.3, 1.5]	1.4–1.7 [m]	1.4–1.7 [m]
t-Leu-**4d**	3.85 [t, 3.1]	4.80 [ddd, 14.0, 5.1, 3.1]	1.4–1.7 [m]	1.4–1.7 [m]
t-Leu-**5d**	4.10 [t, 1.4]	4.78 [ddd, 10.2, 6.7, 1.4]	1.4–1.7 [m]	1.4–1.7 [m]

a) Chemical shifts and coupling constants are shown in δ (ppm) and *J* (Hz), respectively.

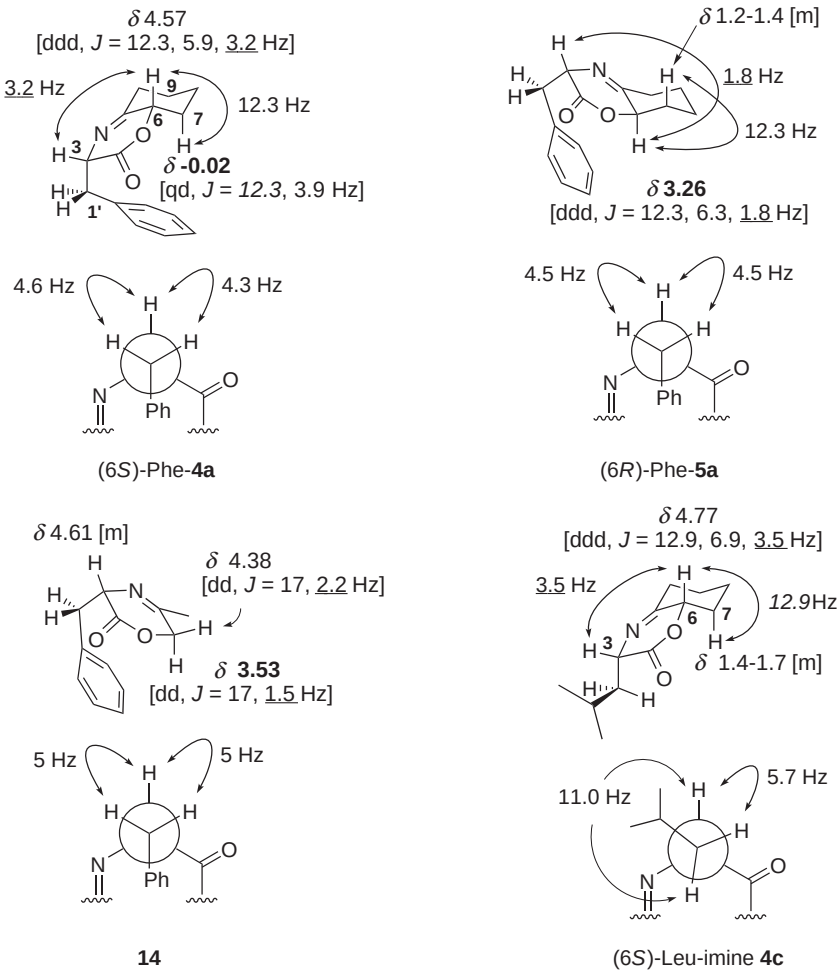
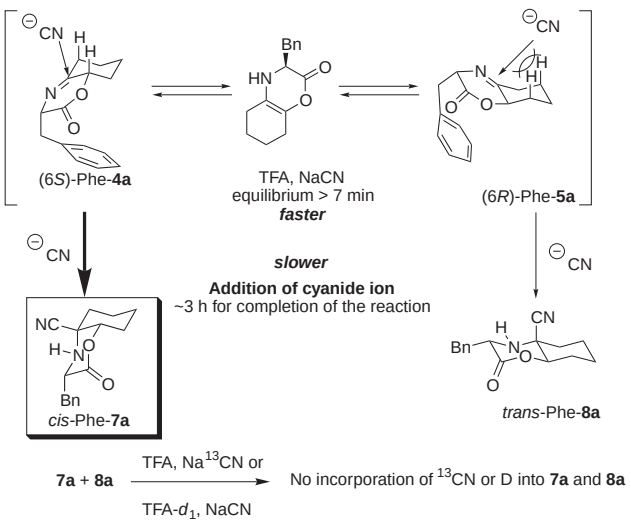
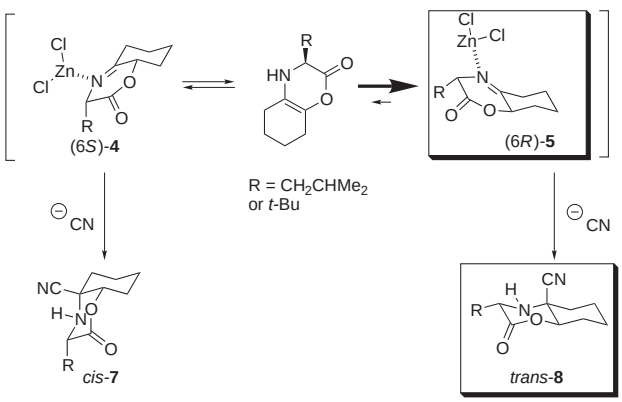


Fig. 1. Proposed conformation of Phe-**4a**, Phe-**5a**, Leu-**4d**, and monocyclic ketimine **14**.



Scheme 4.



Scheme 5.

tion of the (6*R*)-ketimine formation through chelation to the imino group, although its effect on the ketimine conformation can not be verified at this stage. It is noted that dehydration of **3d** having a *t*-Leu ester gave (6*R*)-**5d** as the major ketimine isomer. The bulky *t*-Bu group would restrict the formation of (6*S*)-**4d** due to steric reasons.

Conclusion

We have examined the effects of the chiral auxiliary for the stereoselective synthesis of **1a** and **1b** through exploitation of intermediary ketimine equilibrium and conformations under different reaction conditions. From these experiments, the stereochemical outcome of cyanide addition to a bicyclo[4.4.0]-azaoxaoctane system to form the corresponding α-amino nitrile was clearly understood. On the basis of these studies, we have established a stereoselective route to access each

cis- and *trans*-isomer of the Ahh **1a** and **1b** using an asymmetric version of the Strecker synthesis. Extension of these results for the synthesis of further substituted Ahh derivatives and their incorporation to peptides is in progress.

Experimental

General. All reagents and solvents were purchased from either Aldrich Chemical Company, Inc.; Merck & Co., Inc.; Nacalai Tesque Company, Ltd.; Peptide Institute; Tokyo Kasei Kogyo Co., Ltd.; or Wako Pure Chemical Industries, Ltd.; and used without further purification unless otherwise indicated. Tetrahydrofuran (THF) was distilled under an argon atmosphere from sodium/benzophenone ketyl. Dichloromethane (CH_2Cl_2) was distilled from diphosphorus pentaoxide (P_2O_5). Methanol (MeOH) was distilled from magnesium turnings and iodine. Acetonitrile (CH_3CN) was distilled from calcium hydride (CaH_2). DMSO was distilled under reduced pressure from CaH_2. Diethyl ether (Et_2O) and *N*,*N*-dimethylformamide (DMF) of anhydrous grade were used. ^{1}H NMR spectra were recorded on either a JEOL JNM-LA300 (300 MHz), JEOL JNM-LA400 (400 MHz), or Varian Unity plus 500 spectrometer. Chemical shifts of ^{1}H NMR were reported in parts per million (ppm, δ) relative to tetramethylsilane ($\delta = 0.00$) in $CDCl_3$ or HDO ($\delta = 4.80$) in D_2O, or CD_2HOD ($\delta = 3.30$) in CD_3OD. ^{13}C NMR spectra were recorded on a JEOL JNM-LA300 (75 MHz) or JEOL JNM-LA400 (100 MHz) spectrometer. Chemical shifts of ^{13}C NMR were reported in ppm (δ) relative to $CHCl_3$ ($\delta = 77.0$) in $CDCl_3$, CH_3OH ($\delta = 49.0$) in D_2O or CH_3OH ($\delta = 49.0$) in CD_3OD, or DMSO ($\delta = 39.5$) in DMSO-d_6. Low resolution mass spectra (LRMS) and high resolution mass spectra (HRMS) were obtained on a JEOL JMS-AX500 for fast atom bombardment ionization (FAB), chemical ionization (CI), or electron ionization (EI). Elemental analyses were recorded on a Perkin-Elmer 240C. All reactions were monitored by thin-layer chromatography (TLC), which was performed with precoated plates (silica gel 60 F-254, 0.25 mm layer thickness, manufactured by Merck). TLC visualization was accomplished using UV lump (254 nm) or a charring solution (ethanoic *p*-anisaldehyde, ethanoic molybdophosphoric acid, aqueous potassium permanganate, and butanoic ninhydrin). Daisogel IR-60 1002W(40/63 μm) was used for flash column chromatography on silica gel. Reversed phase chromatography was performed on a Cosmosil® 140C18-PREP. The esters **3a–3d** were prepared according to the procedures reported.[6b]

General Procedure for Formation of Ketimines 4a–4d and 5a–5d from Esters 3a–3d. To a solution of the ester **3** (0.5 mmol) in CH_2Cl_2 was added TFA (1 mL) at 0 °C with stirring. The mixture was stirred at room temperature for 30 min and concentrated in vacuo. The residue was diluted with toluene and concentrated in vacuo. To a solution of the residue in acetonitrile (2 mL) was added Na_2CO_3 (263 mg, 2.5 mmol) and anhydrous $MgSO_4$ (600 mg, 5 mmol) with stirring. The mixture was filtered and the filtrate was concentrated in vacuo to give a mixture of the ketimines **4** and **5** as a pale yellow oil in a ratio as shown in Table 1. Without further purification, the imine was used for the cyanide addition reactions under either condition A or B and for the equilibrium experiments.

(2*S*,4a*R*)- and (2*S*,4a*S*)-2-Benzyl-3,4a,5,6,7,8-hexahydro-2*H*-4-oxaquinolin-3-ones (4a) and (5a) (4a:5a = 1:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.02 (1/2H, qd, $J = 12.3$, 3.9 Hz), 1.20–2.18 (7H, m), 3.50 (1/2H, ddt, $J = 13.5$, 4.3, 1.7 Hz), 2.59 (1/2H, ddt, $J = 14.8$, 4.2, 1.7 Hz), 3.15 (1/2H, dd, $J = 13.3$, 4.5 Hz), 3.24–3.28 (1H, m), 3.36 (1/2H, dd, $J = 13.3$, 4.5 Hz), 3.45 (1/2H, dd, $J = 13.3$, 4.3 Hz), 4.57 (1/2H, ddt, $J = 4.6$, 4.3, 3.2 Hz), 4.57 (1/2H, ddd, $J = 12.3$, 5.9, 3.2 Hz), 4.74 (1/2H, tt, $J = 4.5$, 1.8 Hz), 7.07–7.28 (5H, m). ^{1}H NMR (400 MHz, C_6D_6) δ −0.01 (1/2H, qd, $J = 12.3$, 3.7 Hz), 0.52–1.67 (7H, m), 2.37 (1/2H, m), 2.49 (1/2H, m), 3.08 (1/2H, dd, $J = 13.1$, 4.5 Hz), 3.17 (1/2H, ddd, $J = 12.3$, 6.3, 1.8 Hz), 3.23 (1/2H, dd, $J = 13.2$, 4.3 Hz), 3.37 (1/2H, dd, $J = 13.1$, 4.5 Hz), 3.52 (1/2H, dd, $J = 13.2$, 4.6 Hz), 3.84 (1/2H, ddd, $J = 12.3$, 5.9, 3.2 Hz), 4.38 (1/2H, ddt, $J = 4.6$, 4.3, 3.2 Hz), 4.72 (1/2H, tt, $J = 4.5$, 1.8 Hz), 7.00–7.28 (5H, m).

(2*S*,4a*R*)- and (2*S*,4a*S*)-2-Benzyl-4a-deuterio-3,4a,5,6,7,8-hexahydro-2*H*-4-oxaquinolin-3-ones (12) and (13) (12:13 = 2:1): ^{1}H NMR (400 MHz, 2-propanol-d_8) δ −0.16 (1/2H, qd, $J = 12.3$, 4.1 Hz), 1.02–2.15 (7H, m), 2.42 (1/2H, m), 2.54 (1/2H, m), 3.02 (1/2H, dd, $J = 13.2$, 4.6 Hz), 3.13 (1/2H, dd, $J = 13.2$, 4.6 Hz), 3.20–3.26 (1H, m), 3.32 (1/2H, dd, $J = 13.2$, 4.1 Hz), 4.43 (1/2H, ddt, $J = 4.6$, 4.1, 3.2 Hz), 4.58 (1/2H, m), 4.67 (1/2H, ddd, $J = 12.3$, 5.5, 3.2 Hz), 6.94–7.18 (5H, m).

(2*S*,4a*R*)- and (2*S*,4a*S*)-2-(Indol-3-ylmethyl)-3,4a,5,6,7,8-hexahydro-2*H*-4-oxaquinolin-3-ones (4b) and (5b) (4b:5b = 1:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.21 (1/2H, qd, $J = 12.3$, 4.0 Hz), 0.23 (1/2H, qt, $J = 13.5$, 4.2 Hz), 1.00–2.50 (8H, m), 3.24 (1/2H, ddd, $J = 12.1$, 6.4, 1.5 Hz), 3.37 (1/2H, dd, $J = 14.0$, 4.1 Hz), 3.49–3.53 (1H, m), 3.57 (1/2H, dd, $J = 14.0$, 4.3 Hz), 4.47 (1/2H, ddd, $J = 12.3$, 5.7, 3.5 Hz), 4.61 (1H, tt, $J = 4.3$, 3.5 Hz), 4.77 (1/2H, ddt, $J = 4.3$, 4.1, 1.5 Hz), 6.98–7.34 (4H, m), 7.54 (1/2H, d, $J = 8.1$ Hz), 7.66 (1/2H, d, $J = 8.1$ Hz), 8.16 (1/2H, s), 8.23 (1/2H, s). ^{1}H NMR (400 MHz, C_6D_6) δ −0.32 (1/2H, qd, $J = 12.2$, 3.7 Hz), 0.08 (1/2H, qt, $J = 13.6$, 4.3 Hz), 0.27–1.64 (7H, m), 2.22 (1/2H, dquint, $J = 13.5$, 2.1 Hz), 2.40 (1/2H, dquint, $J = 14.4$, 2.1 Hz), 3.05 (1/2H, ddd, $J = 12.1$, 6.2, 1.8 Hz), 3.33 (1/2H, dd, $J = 14.2$, 4.2 Hz), 3.48 (1/2H, dd, $J = 14.1$, 4.3 Hz), 3.53 (1H, dd, $J = 14.2$, 4.2 Hz), 3.63 (1/2H, dd, $J = 14.1$, 4.3 Hz), 3.72 (1/2H, ddd, $J = 12.2$, 5.6, 3.3 Hz), 4.43 (1/2H, tt, $J = 4.3$, 3.3 Hz), 4.76 (1/2H, tt, $J = 4.2$, 1.8 Hz), 6.62–7.86 (6H, m).

(2*S*,4a*R*)- and (2*S*,4a*S*)-2-(2-Methylpropyl)-3,4a,5,6,7,8-hexahydro-2*H*-4-oxaquinolin-3-ones (4c) and (5c) (4c:5c = 1:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (3/2H, d, $J = 3.5$ Hz), 0.92 (3/2H, d, $J = 3.5$ Hz), 0.92 (3/2H, d, $J = 1.1$ Hz), 0.94 (3/2H, d, $J = 1.1$ Hz), 1.39–2.63 (11H, m), 4.01 (1/2H, ddt, $J = 11.0$, 5.7, 3.5 Hz), 4.30 (1/2H, ddt, $J = 7.8$, 6.3, 1.5 Hz), 4.77 (1/2H, ddd, $J = 12.9$, 6.9, 3.5 Hz), 4.80 (1/2H, ddd, $J = 11.0$, 7.3, 1.5 Hz).

(2*S*,4a*R*)- and (2*S*,4a*S*)-2-(*t*-Butyl)-3,4a,5,6,7,8-hexahydro-2*H*-4-oxaquinolin-3-ones (4d) and (5d) (4d:5d = 21:79): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (27/10H, s), 1.10 (63/10H, s), 1.45–2.72 (8H, m), 3.85 (3/10H, t, $J = 3.1$ Hz), 4.10 (7/10H, t, $J = 1.4$ Hz), 4.78 (7/10H, ddd, $J = 10.2$, 6.7, 1.4 Hz), 4.80 (3/10H, ddd, $J = 14.0$, 5.1, 3.1 Hz).

General Procedure for the Cyanide Addition to a Mixture of Ketimines 4a–4d and 5a–5d: Condition A. To a solution of a mixture of the ketimines **4** and **5** (0.5 mmol) in 2-PrOH (2 mL) was added TFA (39 μL, 0.5 mmol) at room temperature. After stirring for 5 min, NaCN (49 mg, 1 mmol) was added to the reaction mixture. The mixture was stirred for 2 h at room temperature, and then diluted with AcOEt and brine. The organic layer was washed with H_2O, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography to give a mixture of the α-amino nitriles **7** and **8**. The yields and the ratios of the products are shown in Table 1. The ^{1}H NMR data of **7a** and **8a** were identical with those reported.[6d]

Condition B. To a solution of a mixture of the ketimines **4** and **5** (0.5 mmol) in 2-PrOH (2 mL) was added $ZnCl_2$ (0.5 mL in THF solution, 0.5 mmol) at room temperature. The mixture was stirred for 5 min, and then TMSCN (0.2 mL, 1.5 mmol) was added. The mixture was stirred for 2 h at room temperature, and diluted with AcOEt and brine. The organic layer was washed with H_2O, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography to give a mixture of the α-amino nitriles **7** and **8**. The yields and the ratios of the products are shown in Table 1.

(1*S*,3*S*,6*R*)- and (1*S*,3*S*,6*S*)-2-Aza-3-(indol-3-ylmethyl)-5-oxa-4-oxobicyclo[4.4.0]decane-1-carbonitriles (7b) and (8b) (7b:8b = 1:2): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21–2.07 (8H, m), 3.16 (1/3H, dd, J = 14.4, 9.6 Hz), 3.19 (2/3H, dd, J = 14.5, 8.7 Hz), 3.55 (2/3H, dd, J = 14.5, 3.6 Hz), 3.62 (1/3H, ddd, J = 14.4, 3.0, 0.8 Hz), 3.98 (1/3H, dd, J = 12.2, 4.1 Hz), 4.18 (2/3H, dt, J = 8.7, 3.6 Hz), 4.31 (1/3H, dd, J = 9.6, 3.0 Hz), 4.33 (2/3H, dd, J = 10.2, 4.3 Hz), 7.10–7.40 (4H, m), 7.66 (2/3H, d, J = 8.0 Hz), 7.67 (1/3H, d, J = 7.8 Hz), 8.22 (1/3H, brs), 8.23 (2/3H, brs). HRMS (CI^+) m/z calcd for $C_{17}H_{19}N_2O_2$ $(M - CN)^+$ 283.1446, found 283.1443.

(1*S*,3*S*,6*R*)- and (1*S*,3*S*,6*S*)-2-Aza-3-(2-methylpropyl)-5-oxa-4-oxobicyclo[4.4.0]decane-1-carbonitriles (7c) and (8c) (7c:8c = 18:71): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (12/5H, d, J = 6.6 Hz), 0.96 (3/5H, d, J = 6.5 Hz), 0.97 (12/5H, d, J = 6.6 Hz), 0.98 (3/5H, d, J = 6.5 Hz), 1.38–2.17 (11H, m), 3.89 (1/5H, dd, J = 8.8, 4.2 Hz), 4.06 (4/5H, dd, J = 8.4, 4.0 Hz), 4.10 (4/5H, dd, J = 12.2, 4.1 Hz), 4.47 (1/5H, dd, J = 8.8, 4.4 Hz); HRMS (CI^+) m/z calcd for $C_{13}H_{21}N_2O_2$ $(M + H)^+$ 237.1603, found 237.1604.

(1*S*,3*S*,6*R*)- and (1*S*,3*S*,6*S*)-2-Aza-3-(*t*-butyl)-5-oxa-4-oxobicyclo[4.4.0]decane-1-carbonitriles (7d) and (8d) (7d:8d = 5:90): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (15/2H, s), 1.12 (3/2H, s), 1.21–2.15 (8H, m), 3.62 (1/6H, s), 3.75 (5/6H, s), 4.07 (5/6H, dd, J = 12.2, 4.4 Hz), 4.38 (1/6H, dd, J = 10.0, 4.9 Hz); HRMS (CI^+) m/z calcd for $C_{13}H_{21}N_2O_2$ $(M + H)^+$ 237.1603, found 237.1609.

Oxidation of α-Amino Nitrile 7a Using Method A. To a solution of **7a** (1.5 g, 5.57 mmol) in dichloromethane (7 mL) was added *t*-BuOCl (0.8 mL, 6.71 mmol) at 0 °C. After stirring the mixture at 0 °C for 30 min, DABCO (1.5 g, 13.4 mmol) was added. The reaction mixture was stirred at the same temperature for 30 min, quenched by the addition of water, and extracted with ethyl acetate. The organic layer was washed with 1 M HCl, water, brine, dried over anhydrous $MgSO_4$, and then concentrated in vacuo. The residue was purified by flash column chromatography to give **9a** (1.47 g, 97%), whose spectroscopic data were identical to those reported.[4,6]

Oxidation of α-Amino Nitrile 8d Using Method B. Ozone was bubbled through a solution of **8d** (24 mg, 0.10 mmol) in ethyl acetate (7 mL) at −78 °C for 15–30 min (flow rate of O_2: 150 NL h^{-1}, which corresponded to 3 g h^{-1} of O_3). To the mixture was added dimethyl sulfide (1 mL). The mixture was warmed to room temperature, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (elution with hexane/EtOAc = 4:1, then 2:1) to give **10d** (14 mg, 59%) and α-amido nitrile (8 mg, 34%) as a colorless amorphous powder. The mixture without separation was converted to **1b** according to the reported procedure.[9]

(8a*S*,4a*R*)-2-(*t*-Butyl)-3-oxo-4a,5,6,7,8,8a-hexahydro-3*H*-4-oxaquinolin-8a-carbonitrile (10d): $[\alpha]^{28}_D$ −168.5 (*c* 1.06, $CHCl_3$); FTIR (neat) 2952, 2867, 2245, 1747, 1620, 1456, 1360 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54–2.01 (6H, m), 2.20 (1H, m), 2.63 (1H, ddd, J = 13.6, 5.1, 2.9 Hz), 3.94 (1H, dd, J = 11.9, 4.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 153.7, 115.9, 79.6, 59.5, 39.5, 35.8, 28.7, 22.9, 22.3; HRMS (EI) m/z calcd for $C_{13}H_{18}N_2O_2$ $(M)^+$ 234.1368, found 234.1341.

***N*-((1*S*,2*R*)-1-Cyano-2-hydroxycyclohexyl)-2,2-dimethylpropanamide:** $[\alpha]^{25}_D$ +45.8 (*c* 0.48, $CHCl_3$); FTIR (neat) 3408, 3345, 2930, 2245, 1647, 1558, 1539, 1456 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27–1.47 (6H, m), 2.07 (1H, m), 2.82 (1H, m), 3.49 (1H, brs), 3.63 (1H, dd, J = 10.8, 3.5 Hz), 6.17 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.5, 117.6, 74.4, 58.9, 39.2, 34.3, 31.7, 27.4, 23.4, 21.8; HRMS (EI) m/z calcd for $C_{12}H_{20}N_2O_2$ $(M)^+$ 224.1525, found 224.1536.

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