A Synthesis of Chiral 1,1,3-Trisubstituted 1,2,3,4-Tetrahydro-*β*-carbolines by the Pictet–Spengler Reaction of Tryptophan and Ketones: Conversion of (1*R*,3*S*)-Diastereomers into Their (1*S*,3*S*)-Counterparts by Scission of the C(1)–N(2) Bond

Yoshie HORIGUCHI,* Masayoshi NAKAMURA, Toshiaki SAITOH, and Takehiro SANO

Showa Pharmaceutical University; 3–3165, Higashi-tamagawagakuen, Machida, Tokyo 194–8543, Japan.

Received June 18, 2003; accepted September 11, 2003

The Pictet–Spengler cyclization of the imines (3) prepared by the condensation of L-tryptophan methyl ester (1) and aryl methyl ketones (2), using titanium(IV) isopropoxide as an iminating reagent, quantitatively proceeded, when treated with trifluoroacetic acid (TFA) or formic acid, to provide two diastereomers, that is (1*S*,3*S*)-1-aryl-3-isopropoxycarbonyl-1-methyl-1,2,3,4-tetrahydro-*β*-carbolines (4) and their (1*R*,3*S*)-diastereomers (5), of which the diastereomer ratios varied from 1 to 5 depending on the reaction conditions. The (1*R*,3*S*)-diastereomers (5) are thermodynamically more stable than their (1*S*,3*S*)-congeners (4), as shown by equilibration experiments in TFA. The conversion of 4 to 5 (also 5 to 4) should occur under acidic conditions by cleavage of the C(1)–N(2) bond with complete retention of configuration at the C-3 chiral center. The low diastereo-selectivity observed in the Pictet–Spengler reaction of 1 and 2 is concluded to be a stereochemical outcome under conditions of kinetic control (lower temperature, shorter reaction time), while the high diastereo selectivity with preferential formation of the more stable isomer (5) is the result of thermodynamically controlled experiments (higher temperature, longer reaction time).

Key words tetrahydro-*β*-carboline; Pictet–Spengler reaction; stereoselectivity; tryptophan; aryl methyl ketone

The Pictet–Spengler reaction[1] has long been an important reaction for the syntheses of biologically important isoquinolines and *β*-carbolines.[2,3] Recently, we have developed a highly efficient method of synthesizing 1,1-disubstituted tetrahydroisoquinolines[4] and tetrahydro-*β*-carbolines[5] by the Pictet–Spengler reaction of arylethylamines and ketones using titanium(IV) isopropoxide as an iminating reagent. This method has an advantage in that the reaction can be carried out without the isolation of the acid-labile imines under a one-pot procedure. Although the Pictet–Spengler reactions using tryptophan and aldehydes which produce chiral 1,3-disubstitued 1,2,3,4-tetrahydro-*β*-carbolines (TH*β*Cs) have been extensively investigated,[6—12] the reaction with ketone has not been hitherto investigated. Here we describe the Pictet–Spengler reaction of tryptophan methyl ester with aryl methyl ketones, which may provide a convenient method of synthesizing chiral 1,1,3-trisubstituted TH*β*Cs.

Results and Discussions

Pictet–Spengler Reaction of Tryptophan Methyl Ester (1) with Aryl Methyl Ketones (2) The condensation reaction of L-tryptophan methyl ester (**1**) and aryl methyl ketones (**2a**: acetophenone, **2b**: 1-(4-chlorophenyl)-2-ethanone, **2c**: 1-(4-methoxyphenyl)-2-ethanone) to the imine intermediates (**3a**—**c**) was carried out by heating in titanium(IV) isopropoxide at 70 °C for 3 h without using any solvent. To the mixture of the *in situ* formed imines (**3**) was added a large excess amount of trifluoroacetic acid (TFA) or formic acid (HCOOH). The reaction mixture was then allowed to react at 70 °C or at room temperature for appropriate times to complete the Pictet–Spengler cyclization. During the imination, the ester exchange reaction from the methyl ester to the isopropyl ester occurred. The reactions, in all cases, produced two diastereometric 1-aryl-3-isopropoxycarbonyl-1-methyl-TH*β*Cs (**4**) and (**5**) in good total yields (Chart 1, Table 1).

The reaction of **1** and **2a** with TFA at 70 °C for 1 h provided **4a** and **5a** in yields of 10% and 45%, respectively (Table 1, Run 1). The same treatment with TFA at room temperature for 1 h improved the reaction to give higher yields of **4a** (31%) and **5a** (54%) (Table 1, Run 2). When this reaction mixture reacted at room temperature for a longer period of time (18 h), the yields of products decreased slightly (**4a**: 14%, **5a**: 50%) (Table 1, Run 3). The facts indicated that TFA rapidly induced the cyclization and at the same time slowly decomposed the products **4a** and **5a** by long contact with the acid. The reaction with HCOOH also induced the expected cyclization, although it was slow, to give results similar to those of TFA-induced cyclization. Thus, the reaction at 70 °C for 18 h gave **4a** (13%) and **5a** (58%) (Table 1, Run 4), while at room temperature for 18 h the reaction produced **4a** (39%) and **5a** (41%) (Table 1, Run 5).

The reaction of **1** with 1-(4-chlorophenyl)-2-ethanone (**2b**) and 1-(4-methoxyphenyl)-2-ethanone (**2c**) with TFA or HCOOH gave results similar to those of **2a** (**2b**: Table 1, Runs 6—10 and **2c**: Table 1, Runs 11—15).

The structures of products **4** and **5** were readily determined by elementary and spectral analyses (Mass, IR, ^{1}H- and ^{13}C-NMR, $[\alpha]_D$). In the ^{1}H-NMR spectrum of *cis*-diastereomer (**4a**), the signal of 4-H appeared as a double doublet at δ 2.87 (Hax, J=11, 15 Hz) and δ 3.19 (Heq, J=4, 15 Hz) and the signal of 3-H appeared as a double doublet at δ 4.00 (J=4, 11 Hz). The coupling constants (J=4, 15 Hz) between 3-H and 4-H showed that the 3-isopropoxycarbonyl group is in equatorial orientation when the tetrahydro-*β*-carboline ring has a half chair form. In the ^{1}H-NMR spectrum of *trans*-diasteromer (**5a**), a similar signal pattern appeared. The similar coupling constant value (J=5, 11 Hz) between 3-H and 4-H indicated that the 3-isopropoxycarbonyl group of **5a** had the same orientation (equatorial) as **4a**. The stereochemistries of the substituents at the C-1 and C-3 chiral cen-

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* To whom correspondence should be addressed. e-mail: horiguti@ac.shoyaku.ac.jp

Table 1. Pictet–Spengler Reaction of L-Tryptophan Methyl Ester (**1**) with Aryl Methyl Ketones (**2**) Using Titanium(IV) Isopropoxide

Run	Ketones (**2**)		Acids	Conditions		Yields (%) of β-carbolines (THβCs)					Ratio of **5**/**4**[a)]
		R		Temp (°C)	Time (h)	**4** (1*S*,3*S*)		**5** (1*R*,3*S*)		**4**+**5**	
1	**2a**	H	TFA	70	1	**4a**	10	**5a**	45	55	4.5
2	**2a**	H	TFA	rt	1	**4a**	31	**5a**	54	85	1.7
3	**2a**	H	TFA	rt	18	**4a**	14	**5a**	50	64	3.6
4	**2a**	H	HCOOH	70	18	**4a**	13	**5a**	55	71	4.2
5	**2a**	H	HCOOH	rt	18	**4a**	39	**5a**	41	80	1.2
6	**2b**	Cl	TFA	70	1	**4b**	15	**5b**	57	72	3.8
7	**2b**	Cl	TFA	rt	1	**4b**	34	**5b**	46	80	1.4
8	**2b**	Cl	TFA	rt	18	**4b**	14	**5b**	68	82	4.9
9	**2b**	Cl	HCOOH	70	18	**4b**	9	**5b**	44	53	4.9
10	**2b**	Cl	HCOOH	rt	18	**4b**	27	**5b**	37	64	1.4
11	**2c**	OCH_3	TFA	70	1	**4c**	14	**5c**	59	73	4.9
12	**2c**	OCH_3	TFA	rt	1	**4c**	13	**5c**	62	75	4.8
13	**2c**	OCH_3	TFA	rt	18	**4c**	14	**5c**	59	73	4.2
14	**2c**	OCH_3	HCOOH	70	18	**4c**	15	**5c**	47	62	3.1
15	**2c**	OCH_3	HCOOH	rt	18	**4c**	6	**5c**	13	19	2.2

a) The ratios were calculated by the isolated yields of **4** and **5**.

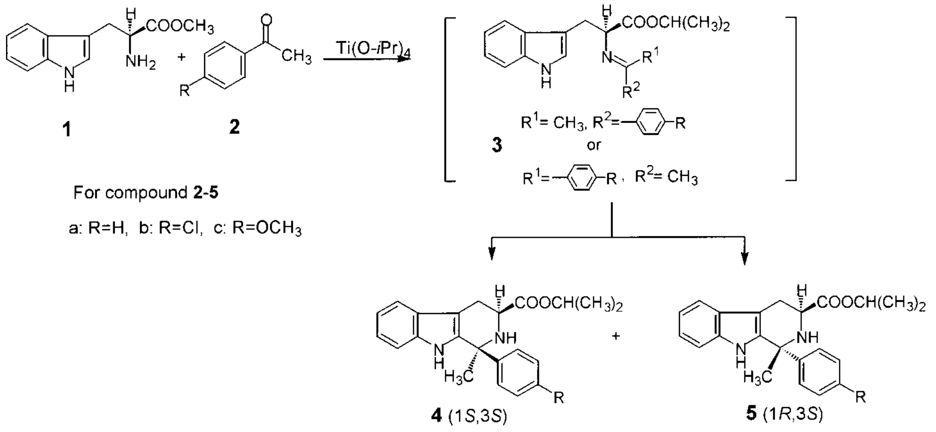

Chart 1

Table 2. ^{1}H- and ^{13}C-NMR Signals (C_1 and C_3) and $[\alpha]_D$ Values of **4** and **5**

THβCs	R	^{1}H-NMR (δ)		^{13}C-NMR (ppm)		$[\alpha]_D$ (*c*) in MeOH
		C_1-CH_3	C_3-H (*J*, Hz)	C_1	C_3	
4a	H	1.92	4.00 (4, 11)	57.0	53.3	−53.3° (1.0)
4b	Cl	1.90	3.99 (4, 11)	56.7	53.3	−45.4° (1.0)
4c	OCH_3	1.89	3.99 (4, 11)	56.5	53.4	−50.1° (1.0)
5a	H	1.86	3.50 (5, 11)	57.0	52.2	−10.0° (1.0)
5b	Cl	1.82	3.45 (5, 11)	56.6	52.2	−14.4° (0.5)
5c	OCH_3	1.84	3.50 (5, 11)	56.5	52.1	−14.6° (1.0)

ters were determined on the basis of 2D-nuclear Overhauser and exchange spectroscopy (NOESY) and difference in nuclear Overhauser effect (DIF-NOE). In the NOESY spectrum of **4a**, the signal of the C-1 methyl proton at δ 1.92 showed a correlation of the C-3 proton at δ 4.00. Irradiation of the C-1 methyl signal caused enhancement of the C-3 proton signal (14%), indicating that the stereochemistry of the C-1 methyl group and the C-3 proton of **4a** is a *cis*-diaxial orientation. In the NOESY spectrum of **5a**, the signal of the C-3 proton at δ 3.50 showed a correlation of the C-1 phenyl proton at δ 7.1—7.9. Irradiation of the C-3 proton signal caused enhancement of the C-1 phenyl signal (17%), indicating that the relative stereochemistry of the C-1 phenyl group and the C-3 proton of **5a** is a *cis*-diaxial orientation. Thus, it was determined that the stereochemistry of the C-1 phenyl group and the C-3 isopropyl ester is *cis* for **4a** (*cis*-diastereomer) and *trans* for **5a** (*trans*-diastereomer). The $[\alpha]_D$ values of **4a** and **5a** obtained by the reaction of runs 1—5 were always consistent (Table 2). This fact strongly suggested that the Pictet–Spengler cyclization did not involve any racemization process. The structures of products **4b**, **4c** and **5b, 5c** from 1-(4-chlorophenyl)- (**2b**) and 1-(4-methoxyphenyl)-2-

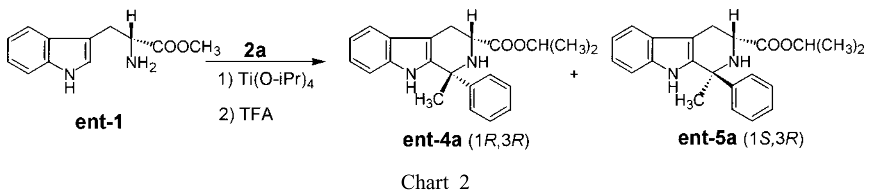

Chart 2

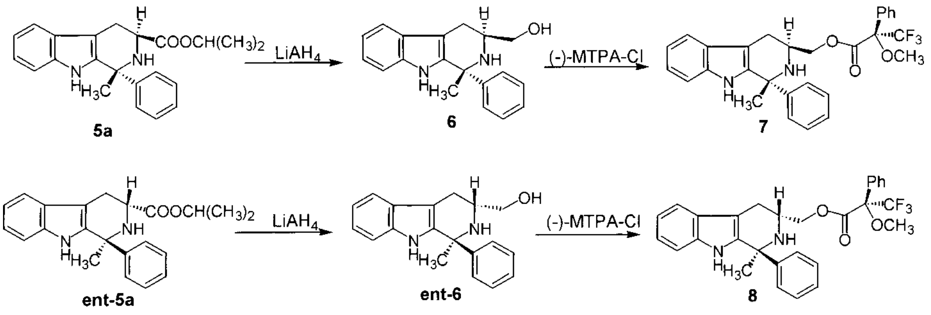

Chart 3

ethanone (**2c**) were readily determined by their analogy in the ^{1}H- and ^{13}C-NMR signals, and optical rotations with those for **4a** and **5a**, respectively (Table 2).

In order to determine whether the L-tryptophan chiral center had been partially racemized before inducing the Pictet–Spengler cyclization, we carried out following experiment. D-Tryptophan methyl ester (**ent-1**) on the Pictet–Spengler reaction with **2a** using TFA at room temperature for 1 h yielded two products, **ent-4a** (24%) ($[\alpha]_D$ +52.7°) and **ent-5a** (38%) ($[\alpha]_D$ +9.9°). Their ^{1}H- and ^{13}C-NMR signals were identical with those of **4a** and **5a**, but the specific optical rotations were opposite in sign (**4a**: $[\alpha]_D$ −53.3°) and (**5a**: $[\alpha]_D$ −10.0°).

The optical purities of **5a** and **ent-5a** were shown to be 100% by the ^{1}H-NMR spectral inspection of the Mosher esters **7** and **8**, which did not show any contamination of their corresponding diastereomers. This fact also supported that the epimerization at the C-3 chiral had not occurred before the Pictet–Spengler cyclization. Thus, the structures of **4a** and **5a**, including the stererocheimstry C-1 and C-3 chiral centers, were assigned to be (1*S*,3*S*)- and (1*R*,3*S*)-3-isopropoxycarbonyl-3-methyl-1-phenyl-TH*β*C, respectively (Chart 3).

Epimerization at C-1 Chiral Center The diastereomer ratio of **5**/**4** in the Pictet–Spengler reactions varied from 1 to 5 depending on such reaction conditions as the nature of acid, temperature, and time, as shown in Table 1. The reaction under more forced conditions showed high diastereo-selectivity, while the reaction under milder conditions gave low diastereo-selectivity. For example, the ratio of **5a**/**4a** in the reaction of **2a** with HCOOH at 70 °C for 18 h is 4.2 (Table 1, Run 4), while the ratio of **5a**/**4a** in the reaction at room temperature for 18 h is 1.2 (Table 1, Run 5). The Pictet–Spengler reactions of **2b** and **2c** gave stereochemical outcomes similar to those of **2a**. The facts clearly demonstrated that the acid-induced cyclization of the imine intermediate (**3**) occurred in a non-diastereoselective manner to yield the *cis*-diastereomer (**4**) and *trans*-diastereomer (**5**) in about a 1 : 1 ratio, then the *cis*-diastereomer (**4**) was converted into the *trans* isomer (**5**) by acid-induced isomerization.

Table 3. TFA-Induced Isomerization of TH*β*Cs (**4**) and (**5**)[a]

Run	TH*β*Cs	R	Conditions		Ratio of **5**/**4**[b]
			Temp (°C)	Time	
1	**4a**	H	rt	1 h	1.4
2	**4a**	H	rt	3 h	3.0
3	**4b**	Cl	rt	1 h	0.8
4	**4b**	Cl	rt	3 h	3.0
5	**4c**	OCH_3	rt	20 min	3.0
6	**4c**	OCH_3	rt	1 h	3.0
7	**5a**	H	rt	3 h	4.0
8	**5b**	Cl	rt	3 h	10.0
9	**5b**	Cl	rt	18 h	4.5
10	**5c**	OCH_3	rt	20 min	4.0

a) The products **4** and **5** were quantitatively recovered and no other products were detected by the TLC inspections. *b*) The ratios were measured by the intensity of the C_3-H signal.

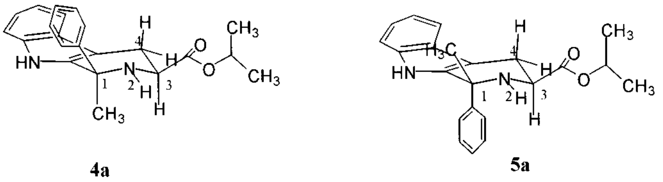

Fig. 1. Most Stable Comformer of **4a** and **5a** Optimized by AM1

The pure *cis*-diastereomer (**4**), when treated with TFA at room temperature for the appropriate times, caused the isomerization to form a 1 : 3 mixture of **4** and **5** in a quantitative yield. The *trans*-diastereomer (**5**) on similar reactions with TFA also quantitatively produced the mixture of **4** and **5** in about a 1 : 4 ratio, as shown in Table 3. These experiments revealed that the *trans*-diastereomer (**5**) is thermodynamically more stable than the *cis*-diastereomer (**4**). The ^{1}H-NMR spectra as described above showed that the *cis*- (**4a**) and *trans*-diastereomer (**5a**) adopts half-chair conformations with 3-equatorial isopropoxycarbonyl groups, as shown in Fig. 1. Using their conformation, we calculated the heat of formation of **4a** and **5a** by AM1 theory, which showed that **5a** is more stable ($\Delta H_f = -9.71$ kcal/mol) than **4a** ($\Delta H_f =$

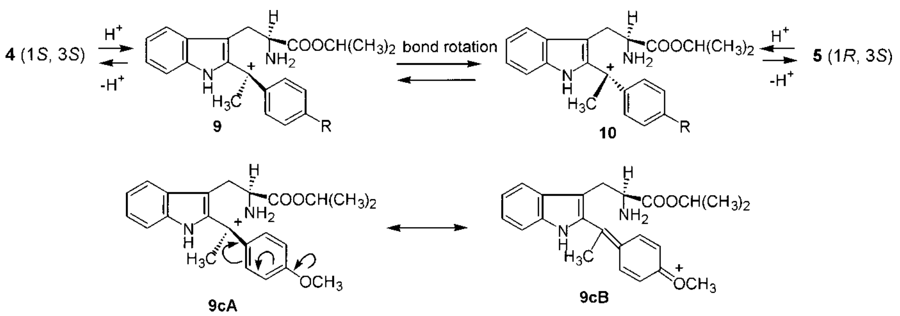

Chart 4

-6.17 kcal/mol), supporting the conclusion obtained from the isomerization experiments.

Furthermore, either the *cis*-isomer (**4**) or the *trans*-isomer (**5**) recovered after this isomerization reaction showed $[\alpha]_D$ values and signs identical with those of the starting materials, indicating that the racemization of either **4** or **5** did not occur.

The TFA-induced epimerization at the C-1 chiral center is able to occur *via* two processes; a) the recombination of the imines (**3**) generated by a retro-Pictet–Spengler reaction, and b) the C(1)–N(2) bond fission-recombination. The mechanism of the retro-Pictet–Spengler reaction can be discarded since in the product of the isomerization experiments described above, there is no indication of the formation of the acid-labile imines (**3**) that readily produce tryptophan isopropyl ester and aryl methyl ketone.

The facts described above, in turn, supported the C(1)–N(2) bond fission-recombination mechanism proposed by Zhang[13,14] and Cook[12] for the epimerization at the C-1 chiral center of 1,3-disubstituted THβC. That is, the epimerization is able to occur *via* the carbocation **9** and its rotatory isomer **10** formed by the acid-induced cleavage of the C(1)–N(2) bond (Chart 4). This epimerization mechanism is consistent with the fact that the 4-methoxyphenyl derivatives (**4c**, **5c**) isomerized more rapidly than phenyl (**4a**, **5a**) or 4-chlorophenyl derivatives (**4b**, **5b**). The methoxy moiety would help to stabilize the carbocation **9cA** *via* the resonance form **9cB**, and therefore to facilitate not only the cleavage of the C(1)–N(2) bond but also the epimerization of the C-1 chiral center.

It is concluded that the low diastereo-selectivity observed in the Pictet–Spengler reaction of **1** and **2** is the stereochemical outcome based on conditions of kinetic control, and that the higher stereoselectivity with the preferential formation of the *trans*-diastereomer (**5**) is the result of the thermodynamic control experiment.

Experimental

Unless otherwise noted, the following procedures were adopted. Melting points were taken on a Yanagimoto SP-M1 hot-stage melting point apparatus and are uncorrected. IR spectra were measured as films for oils and gums, and on KBr disks for solids with a HORIBA FT-710 spectrophotometer, and the values are given in $\mathrm{cm^{-1}}$. NMR spectra were measured on a JEOL JNM-AL300 (^{1}H-NMR: 300 MHz, ^{13}C-NMR: 75 MHz) or a JEOL JNM α500 (^{1}H-NMR: 500 MHz, ^{13}C-NMR: 125 MHz) NMR spectrometer in $\mathrm{CDCl_3}$ with tetramethylsilane as an internal standard, and the chemical shifts are given in δ values. Low-resolution electron impact ionization mass spectra (LR-EI-MS) were taken on a JEOL JMS-AM20 mass spectrometer at 70 eV using a direct inlet probe. High-resolution electron impact ionization mass spectra (HR-EI-MS) were taken on a JEOL JMS-D300 mass spectrometer at 70 eV using a direct inlet probe. Elemental analyses were recorded on a Yanaco CHN-corder MT-3. Optical rotations were determined using a JASCO DIP-1000 digital polarimeter in MeOH. TLC was performed on Merck precoated Silica gel 60 $\mathrm{F_{254}}$ plates. Column chromatography was carried out with silica gel (Wakogel C-200). The organic extract from each reaction mixture was washed with brine, dried over anhydrous $\mathrm{Na_2SO_4}$, and concentrated *in vacuo* to dryness.

The Pictet–Spengler Reaction of L-Tryptophan methyl ester with Acetophenone (2a): Typical procedure L-Tryptophan methyl ester hydrochloride (**1**) (1.2 g, 4.59 mmol) in $\mathrm{H_2O}$ (50 ml) was basified with 10% $\mathrm{K_2CO_3}$ solution and extracted with AcOEt. After removal of the solvent *in vacuo*, the residue was mixed with **2a** (0.46 g, 3.83 mmol) and Ti(O-*i*Pr)$_4$ (1.63 g, 5.75 mmol), and the mixture was heated at 70 °C for 3 h under an argon atmosphere. To the reaction mixture was added the mixture of TFA (43.6 g, 0.383 mol) and trifluoroacetic anhydride (0.8 g, 3.83 mmol) at 0 °C, then the mixture was heated at 70 °C for 1 h. The reaction mixture was diluted with MeOH (100 ml) and passed through a short $\mathrm{SiO_2}$ column (MeOH) to remove $\mathrm{TiO_2}$. The eluent was concentrated *in vacuo* (*ca.* 30 ml) and the residue was neutralized with 10% NaOH solution and extracted with $\mathrm{CHCl_3}$. After removal of the solvent of the extract *in vacuo*, the residue was purified by column chromatography over $\mathrm{SiO_2}$ (benzene–acetone$=$30 : 1) to give **4a** (111 mg, 10%) and **5a** (600 mg, 45%).

(1*S*,3*S*)-3-Isopropoxycarbonyl-1-methyl-1-phenyl-1,2,3,4-tetrahydro-β-carboline (**4a**): Colorless prisms recrystallized from $\mathrm{Et_2O}$–hexane, mp 184—185 °C. IR: 3374, 3343, 2977, 1735, 1710. UV: 279.0 (8800). ^{1}H-NMR: 1.30 (3H, d, J=7 Hz, $\mathrm{CH(C\underline{H}_3)_2}$), 1.32 (3H, d, J=7 Hz, $\mathrm{CH(C\underline{H}_3)_2}$), 1.92 (3H, s, $\mathrm{C\underline{H}_3}$), 2.87 (1H, dd, J=11, 15 Hz, 4-H), 3.19 (1H, dd, J=4, 15 Hz, 4-H), 4.00 (1H, dd, J= 4, 11 Hz, 3-H), 5.11 (1H, m, $\mathrm{C\underline{H}(CH_3)_2}$), 7.1—7.6 (10H, m, Ph-H, Ar-H). ^{13}C-NMR: 21.8 (2×$\mathrm{CH(\underline{C}H_3)_2}$), 25.7 ($\mathrm{\underline{C}H_3}$), 26.4 (C4), 53.3 (C3), 57.0 (C1), 68.6 ($\mathrm{\underline{C}H(CH_3)_2}$), 108.1 (C4a), 110.9 (C8), 118.3 (C6), 119.5 (C5), 121.9 (C7), 126.9 (C4b), 127.0 (2×Ph$\underline{\mathrm{C}}$H), 127.8 (Ph$\underline{\mathrm{C}}$H), 128.6 (2×Ph$\underline{\mathrm{C}}$H), 136.0 (Ph$\underline{\mathrm{C}}$), 139.1 (C9a), 145.3 (C8a), 172.9 ($\underline{\mathrm{C}}$OO). LR-EI-MS: *m/z* 348 ($\mathrm{M^+}$), 245 (base peak). HR-EI-MS: Calcd for $\mathrm{C_{22}H_{24}N_2O_2}$: 348.1835. Found: 348.1817. *Anal.* Calcd for $\mathrm{C_{22}H_{24}N_2O_2}$: C, 75.83; H, 6.94; N, 8.04. Found: C, 75.94; H, 7.07; N, 8.08. $[\alpha]_D$ $-53.3°$ (c=1.0 in MeOH).

(1*R*,3*S*)-3-Isopropoxycarbonyl-1-methyl-1-phenyl-1,2,3,4-tetrahydro-β-carboline (**5a**): Colorless needles recrystallized from $\mathrm{Et_2O}$–hexane, mp 175—176 °C. IR: 3369, 2979, 1724, 1654. UV: 278.5 (8500). ^{1}H-NMR: 1.24 (3H, d, J=6 Hz, $\mathrm{CH(C\underline{H}_3)_2}$), 1.27 (3H, d, J=6 Hz, $\mathrm{CH(C\underline{H}_3)_2}$), 1.86 (3H, s, $\mathrm{C\underline{H}_3}$), 2.82 (1H, dd, J=11, 15 Hz, 4-H), 3.01 (1H, dd, J=5, 15 Hz, 4-H), 3.50 (1H, dd, J=5, 11 Hz, 3-H), 5.06 (1H, sep, J=6 Hz, $\mathrm{C\underline{H}(CH_3)_2}$), 7.1—7.9 (10H, m, Ph-H, Ar-H). ^{13}C-NMR: 21.7 ($\mathrm{CH(\underline{C}H_3)_2}$), 21.8 ($\mathrm{CH(\underline{C}H_3)_2}$), 25.9 (C4), 29.3 ($\mathrm{\underline{C}H_3}$), 52.2 (C3), 57.0 (C1), 68.5 ($\mathrm{\underline{C}H(CH_3)_2}$), 108.8 (C4a), 110.9 (C8), 118.4 (C6), 119.7 (C5), 122.0 (C7), 126.5 (2×Ph$\underline{\mathrm{C}}$H), 127.1(C4b), 127.2 (Ph$\underline{\mathrm{C}}$H), 128.2 (2×Ph$\underline{\mathrm{C}}$H), 135.9 (Ph$\underline{\mathrm{C}}$), 137.4 (C9a), 145.9 (C8a), 173.1 ($\underline{\mathrm{C}}$OO). LR-EI-MS: *m/z* 348 ($\mathrm{M^+}$), 218 (base peak). HR-EI-MS: Calcd for $\mathrm{C_{22}H_{24}N_2O_2}$: 348.1838. Found: 348.1863. *Anal.* Calcd for $\mathrm{C_{22}H_{24}N_2O_2}$: C, 75.83; H, 6.94; N, 8.04. Found: C, 75.74; H, 6.98; N, 8.05. $[\alpha]_D$ $-10.0°$ (c=1.0 in MeOH).

The Pictet–Spengler Reaction of 1 with 2b The reaction of **1** (4.59 mmol) and **2b** (590 mg, 3.83 mmol) under the condition described in Table 1 (Run 6) gave **4b** (490 mg, 34%) and **5b** (670 mg, 46%).

(1*S*,3*S*)-1-(4-Chlorophenyl)-3-isopropoxycarbonyl-1-methyl-1,2,3,4-tetrahydro-β-carboline (**4b**): Colorless needles recrystallized from $\mathrm{Et_2O}$–hexane, mp 195—197 °C. IR: 3384, 3342, 2979, 2935, 1718. ^{1}H-NMR: 1.30 (3H, d, J=6 Hz, $\mathrm{CH(C\underline{H}_3)_2}$), 1.32 (3H, d, J=6 Hz, $\mathrm{CH(C\underline{H}_3)_2}$), 1.90 (3H, s, $\mathrm{C\underline{H}_3}$), 2.86 (1H, dd, J=11, 15 Hz, 4-H), 3.19 (1H, dd, J=4, 15 Hz, 4-H), 3.99 (1H, dd, J=4, 11 Hz, 3-H), 5.12 (1H, sep, J=6 Hz, $\mathrm{C\underline{H}(CH_3)_2}$), 7.1—

7.6 (9H, m, Ar-H, Ph-H). ^{13}C-NMR: 21.8 ($2\times CH(\underline{C}H_3)_2$), 25.6 ($\underline{C}H_3$), 26.2 (C4), 53.3 ($\underline{C}H(CH_3)_2$), 56.7 (C1), 68.7 ($\underline{C}H(CH_3)_2$), 108.3 (C4a), 110.9 (C5), 118.4 (C8), 119.7 (C6), 122.1 (C7), 126.8 (C4b), 128.6 ($2\times Ph\underline{C}H$), 128.7 ($2\times Ph\underline{C}H$), 133.7 ($Ph\underline{C}$), 136.1 ($Ph\underline{C}$), 138.4 (C9a), 144.0 (C8a), 172.8 ($\underline{C}OO$). LR-EI-MS: *m/z* 382, 384 (M$^+$), 367 (base peak). HR-EI-MS: Calcd for $C_{22}H_{23}N_2O_2Cl$: 382.1448, 384.1416. Found: 382.1469, 384.1411. *Anal.* Calcd for $C_{22}H_{23}N_2O_2Cl$: C, 69.01; H, 6.05; N, 7.32. Found: C, 68.84; H, 6.19; N, 7.30. $[\alpha]_D$ −45.4° (c=1.0 in MeOH).

(1*R*,3*S*)-1-(4-Chlorophenyl)-3-isopropoxycarbonyl-1-methyl-1,2,3,4-tetrahydro-*β*-carboline (**5b**): Colorless needles recrystallized from Et$_2$O–AcOEt, mp 245—247 °C. IR: 3417, 3349, 2975, 1720. ^{1}H-NMR: 1.25 (3H, d, J=6 Hz, $CH(C\underline{H}_3)_2$), 1.28 (3H, d, J=6 Hz, $CH(C\underline{H}_3)_2$), 1.82 (3H, s, $C\underline{H}_3$), 2.80 (1H, dd, J=11, 15 Hz, 4-H), 3.08 (1H, dd, J=5, 15 Hz, 4-H), 3.45 (1H, dd, J=5, 11 Hz, 3-H), 5.06 (1H, sep, J=6 Hz, $C\underline{H}(CH_3)_2$), 7.1—7.6 (8H, m, Ph-H, Ar-H), 7.94 (1H, br s, Ar-N$\underline{H}$). ^{13}C-NMR: 21.7 ($CH(\underline{C}H_3)_2$), 21.8 ($CH(\underline{C}H_3)_2$), 25.9 (C4), 29.2 ($\underline{C}H_3$), 52.2 (C3), 56.6 (C1), 68.6 ($CH(CH_3)_2$), 108.9 (C4a), 111.0 (C8), 118.5 (C6), 119.8 (C5), 122.3 (C7), 127.0 (C4b), 128.0 ($2\times Ph\underline{C}H$), 128.3 ($2\times Ph\underline{C}H$), 133.1 (PhC), 135.9 (PhC), 136.9 (C9a), 144.5 (C8a), 173.1 ($\underline{C}OO$). LR-EI-MS: *m/z* 382, 384 (M$^+$), 367 (base peak). HR-EI-MS: Calcd for $C_{22}H_{23}N_2O_2Cl$: 382.1446, 384.1418. Found: 382.1430, 384.1420. *Anal.* Calcd for $C_{22}H_{23}N_2O_2Cl$: C, 69.01; H, 6.05; N, 7.32. Found: C, 68.75; H, 6.10; N, 7.35. $[\alpha]_D$ −14.4° (c=0.5 in MeOH).

The Pictet–Spengler Reaction of 1 with 2c The reaction of **1** (4.59 mmol) and **2c** (570 mg, 3.83 mmol) under the condition described in Table 1 (Run 11) gave **4c** (183 mg, 13%) and **5c** (892 mg, 62%).

(1*S*,3*S*)-3-Isopropoxycarbonyl-1-(4-methoxyphenyl)-1-methyl-1,2,3,4-tetrahydro-*β*-carboline (**4c**): Colorless needles recrystallized from Et$_2$O–hexane, mp 125—127 °C. IR: 3378, 2977, 1724, 1608. ^{1}H-NMR: 1.30 (3H, d, J=6 Hz, $CH(C\underline{H}_3)_2$), 1.31 (3H, d, J=6 Hz, $CH(C\underline{H}_3)_2$), 1.89 (3H, s, $C\underline{H}_3$), 2.85 (1H, dd, J=11, 15 Hz, 4-H), 3.18 (1H, dd, J=4, 15 Hz, 4-H), 3.79 (3H, s, $OC\underline{H}_3$), 3.99 (1H, dd, J=4, 11 Hz, 3-H), 5.11 (1H, sep, J=6 Hz, $C\underline{H}(CH_3)_2$), 6.8—6.9 (2H, m, Ph-H), 7.1—7.2, 7.5—7.6 (total 4H, m, Ar-H), 7.3—7.4 (2H, m, Ph), 7.44 (1H, br s, Ar-N$\underline{H}$). ^{13}C-NMR: 21.8 ($2\times CH(\underline{C}H_3)_2$), 25.8 ($\underline{C}H_3$), 26.4 (C4), 53.4 (C3), 55.3 ($O\underline{C}H_3$), 56.5 (C1), 68.5 ($\underline{C}H(CH_3)_2$), 108.0 (C4a), 110.9 (C8), 113.8 ($2\times Ph\underline{C}H$), 118.2 (C6), 119.5 (C5), 121.9 (C7), 127.0 (C4b), 128.3 ($2\times Ph\underline{C}H$), 136.0 ($Ph\underline{C}$), 137.5 (C9a), 139.3 (C8a), 159.0 ($Ph\underline{C}$), 172.9 ($\underline{C}OO$). LR-EI-MS: *m/z* 378 (M$^+$), 363 (base peak). HR-EI-MS: Calcd for $C_{23}H_{26}N_2O_3$: 378.1944. Found: 378.1979. *Anal.* Calcd for $C_{23}H_{26}N_2O_3$: C, 72.99; H, 6.92; N, 7.40. Found: C, 72.74; H, 7.02; N, 7.31. $[\alpha]_D$ −50.1° (c=1.0 in MeOH).

(1*R*,3*S*)-3-Isopropoxycarbonyl-1-(4-methoxyphenyl)-1-methyl-1,2,3,4-tetrahydro-*β*-carboline (**5c**): Colorless needles recrystallized from Et$_2$O–hexane, mp 178—180 °C. IR: 3369, 2979, 1724, 1608. ^{1}H-NMR: 1.24 (3H, d, J=6 Hz, $CH(C\underline{H}_3)_2$), 1.28 (3H, d, J=6 Hz, $CH(C\underline{H}_3)_2$), 1.84 (3H, s, $C\underline{H}_3$), 2.81 (1H, dd, J=11, 15 Hz, 4-H), 3.09 (1H, dd, J=5, 15 Hz, 4-H), 3.50 (1H, dd, J=5, 11 Hz, 3-H), 3.76 (3H, s, $OC\underline{H}_3$), 5.06 (1H, sep, J=6 Hz, $C\underline{H}(CH_3)_2$), 6.8—6.9 (2H, m, Ph-H), 7.1—7.2 (4H, m, Ar-H), 7.3—7.6 (2H, m, Ph-H), 7.88 (1H, br s, Ar-N$\underline{H}$). ^{13}C-NMR: 21.7 ($CH(\underline{C}H_3)_2$), 21.8 ($CH(\underline{C}H_3)_2$), 25.9 (C4), 29.3 ($\underline{C}H_3$), 52.1 (C3), 55.2 ($O\underline{C}H_3$), 56.5 (C1), 68.4 ($\underline{C}H(CH_3)_2$), 108.6 (C4a), 110.9 (C8), 113.4 ($2\times Ph\underline{C}H$), 118.4 (C6), 119.6 (C5), 122.0 (C7), 127.1 (C4b), 127.7 ($2\times Ph\underline{C}H$), 135.9 ($Ph\underline{C}$), 137.6 (C9a), 138.0 (C8a), 158.6 (PhC), 173.2 ($\underline{C}OO$). LR-EI-MS: *m/z* 378 (M$^+$), 149 (base peak). HR-EI-MS: Calcd for $C_{23}H_{26}N_2O_3$: 378.1944. Found: 378.1964. *Anal.* Calcd for $C_{23}H_{26}N_2O_3$: C, 72.99; H, 6.92; N, 7.40. Found: C, 72.94; H, 7.00; N, 7.36. $[\alpha]_D$ −14.6° (c=1.0 in MeOH).

The Pictet–Spengler Reaction of D-Tryptophan Methyl Ester with 2a D-Tryptophan methyl ester hydrochloride (**ent-1**) (1.2 g, 4.59 mmol) in H$_2$O (50 ml) was basified with 10% K$_2$CO$_3$ solution and extracted with AcOEt. After removal of the solvent *in vacuo*, the residue was mixed with **2a** (0.46 g, 3.83 mmol) and Ti(O-*i*Pr)$_4$ (1.63 g, 5.75 mmol), then the mixture was heated at 70 °C for 3 h under an argon atmosphere. To the reaction mixture was added a mixture of TFA (43.6 g, 0.383 mol) and trifluoroacetic anhydride (0.8 g, 3.83 mmol) at 0 °C, then the mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with MeOH (100 ml) and passed through a short SiO$_2$ column (MeOH) to remove TiO$_2$. The eluent was concentrated *in vacuo* (*ca.* 30 ml) and the residue was neutralized with 10% NaOH solution and extracted with CHCl$_3$. After removal of the solvent *in vacuo*, the residue was purified by column chromatography over SiO$_2$ (benzene–acetone=30 : 1) to give **ent-4a** (315 mg, 24%) and **ent-5a** (505 mg, 38%), respectively.

(1*R*,3*R*)-3-Isopropoxycarbonyl-1-methyl-1-phenyl-1,2,3,4-tetrahydro-*β*-carboline (**ent-4a**): Colorless prisms recrystallized from Et$_2$O–hexane, mp 186—187 °C. IR, ^{1}H- and ^{13}C-NMR were identical with those of **4a**. LR-EI-MS: *m/z* 348 (M$^+$), 333 (base peak). HR-EI-MS: Calcd for $C_{22}H_{24}N_2O_2$: 348.1838. Found: 348.1859. *Anal.* Calcd for $C_{22}H_{24}N_2O_2$: C, 75.83; H, 6.94; N, 8.04. Found: C, 75.77; H, 7.06; N, 8.06. $[\alpha]_D$ +52.7° (c=1.0 in MeOH).

(1*S*,3*R*)-3-Isopropoxycarbonyl-1-methyl-1-phenyl-1,2,3,4-tetrahydro-*β*-carboline (**ent-5a**): Colorless needles recrystallized from Et$_2$O–hexane, mp 170—172 °C. IR, ^{1}H- and ^{13}C-NMR were identical with those of **5a**. LR-EI-MS: *m/z* 348 (M$^+$), 333 (base peak). HR-EI-MS: Calcd for $C_{22}H_{24}N_2O_2$: 348.1835. Found: 348.1829. *Anal.* Calcd for $C_{22}H_{24}N_2O_2$: C, 75.83; H, 6.94; N, 8.04. Found: C, 75.75; H, 7.13; N, 7.90. $[\alpha]_D$ +9.9° (c=1.0 in MeOH).

Reduction of 5a with LiAlH$_4$: Typical Procedure LiAlH$_4$ (22 mg, 0.575 mmol) was added to a solution of **5a** (200 mg, 0.575 mmol) in THF (10 ml) at 0 °C, then the mixture was stirred for 2.5 h at the same temperature. Water was added to the reaction mixture and the mixture was extracted with CHCl$_3$. After removal of the solvent, the residue was purified by column chromatography over SiO$_2$ (AcOEt–hexane=4 : 1) to give (1*R*,3*S*)-3-hydoxymethyl-1-methyl-1-phenyl-1,2,3,4-tetrahydro-*β*-carboline (**6**) (154 mg, 92%) as a colorless gum. IR: 3397, 3291, 2969, 2925. ^{1}H-NMR: 1.80 (3H, s, $C\underline{H}_3$), 2.47 (1H, dd, J=11, 15 Hz, 4-H), 2.70 (1H, dd, J=4, 15 Hz, 4-H), 2.9—3.0 (1H, m, 3-H), 3.48 (1H, dd, J=9, 11 Hz, $C\underline{H}_2OH$), 3.69 (1H, dd, J=4, 11 Hz, $C\underline{H}_2OH$), 7.1—7.5 (9H, m, Ar-H, Ph-H), 7.99 (1H, br s, Ar-N$\underline{H}$). ^{13}C-NMR: 24.7 (C4), 29.8 ($\underline{C}H_3$), 51.2 (C3), 57.3 (C1), 66.0 ($\underline{C}H_2OH$), 109.3 (C4a), 110.9 (C8), 118.4 (C6), 119.6 (C5), 122.0 (C7), 126.6 ($2\times Ph\underline{C}H$), 127.1 (C4a), 128.2 ($2\times Ph\underline{C}H$), 135.9 ($Ph\underline{C}$), 138.1 (C9a), 146.1 (C8a). LR-EI-MS: *m/z* 292 (M$^+$), 277 (base peak). HR-EI-MS: Calcd for $C_{19}H_{20}N_2O$: 292.1573. Found: 292.1572. $[\alpha]_D$ +38.0° (c=0.5 in MeOH).

Reduction of ent-5a with LiAlH$_4$ Reduction of **ent-5a** (200 mg, 0.575 mmol) with LiAlH$_4$ (22 mg, 0.575 mmol) and purification by column chromatography over SiO$_2$ (benzene–acetone=3 : 1) gave (1*R*,3*R*)-3-hydoxymethyl-1-methyl-1-phenyl-1,2,3,4-tetrahydro-*β*-carboline (**ent-6**) (140 mg, 83%) as a colorless gum. IR, ^{1}H- and ^{13}C-NMR were identical with those of **6**. LR-EI-MS: *m/z* 292 (M$^+$), 277 (base peak). HR-EI-MS: Calcd for $C_{19}H_{20}N_2O$: 292.1573. Found: 292.1558. $[\alpha]_D$ −39.7° (c=0.5 in MeOH).

Synthesis of (1*R*,3*S*)-(1-Methyl-1-phenyl-1,2,3,4-tetrahydro-*β*-carboline-3-yl)methyl (*R*)-*α*-Methoxy-*α*-trifluoromethylphenyl Acetate (7): Typical Procedure A solution of **6** (42 mg, 0.144 mmol), pyridine (1.7 ml), DMAP (7 mg) and (−)-MTPA-Cl (90 mg, 0.360 mmol) in CCl$_4$ (3.5 ml) was stirred at room temperature for 24 h under an argon atmosphere. The reaction mixture was diluted with water and the mixture was extracted with CHCl$_3$. After removal of the solvent *in vacuo*, the residue was purified by column chromatography over SiO$_2$ (AcOEt–hexane=4 : 1) to give **7** (48 mg, 66%) as a pale yellow gum. IR: 3058, 2965, 2921, 1745. ^{1}H-NMR: 1.69 (3H, s, $C\underline{H}_3$), 2.57 (1H, dd, J=11, 15 Hz, 4-H), 2.73 (1H, dd, J=5, 15 Hz, 4-H), 3.1—3.2 (1H, m, 3-H), 3.46 (3H, d, J=1 Hz, $OC\underline{H}_3$), 4.32 (1H, dd, J=7, 11 Hz, $C\underline{H}_2O$), 4.45 (1H, dd, J=4, 11 Hz, $C\underline{H}_2O$), 7.1—7.6 (14H, m, 2×Ph-H, Ar-H), 7.91 (1H, br s, Ar-N$\underline{H}$). ^{13}C-NMR: 24.8 (C4), 29.5 ($\underline{C}H_3$), 48.2 (C3), 55.4 (C1), 57.2 ($O\underline{C}H_3$), 69.5 ($\underline{C}H_2O$), 84.7 ($\underline{C}$–CF_3), 108.7 (C4b), 110.9 (C8), 118.3 (C6), 119.6 (C5), 122.0 (C7), 126.4 ($2\times Ph\underline{C}H$), 127.0 (C4a), 127.1 ($Ph\underline{C}H$), 127.4 ($2\times Ph\underline{C}H$), 128.1 ($2\times Ph\underline{C}H$), 128.4 ($2\times Ph\underline{C}H$), 129.7 ($Ph\underline{C}H$), 132.1 ($Ph\underline{C}$), 135.9 (C9a), 137.6 (C8a), 146.0 ($Ph\underline{C}$), 166.5 (s, O–$\underline{C}$O). LR-EI-MS: *m/z* 508 (M$^+$), 58 (base peak). HR-EI-MS: Calcd for $C_{29}H_{27}N_2O_3F_3$: 508.1972. Found: 508.1952.

Synthesis of (1*S*,3*R*)-(1-Methyl-1-phenyl-1,2,3,4-tetrahydro-*β*-carboline-3-yl)methyl (*R*)-*α*-Methoxy-*α*-trifluoromethylphenyl Acetate (8) **8** (54 mg, 89%) was obtained from the reaction of **ent-6** (35 mg, 0.120 mmol) and (−)-MTPA-Cl (90 mg, 0.360 mmol) after purification by column chromatography over SiO$_2$ (AcOEt–hexane=1 : 1) as a pale yellow gum. IR: 3407, 2962, 2919, 1751. ^{1}H-NMR: 1.73 (3H, s, $C\underline{H}_3$), 2.56 (1H, dd, J=11, 15 Hz, 4-H), 2.71 (1H, dd, J=4, 15 Hz, 4-H), 3.08 (1H, m, 3-H), 3.46 (3H, d, J=1 Hz, $OC\underline{H}_3$), 4.33 (1H, dd, J=7, 11 Hz, $C\underline{H}_2O$), 4.39 (1H, dd, J=4, 11 Hz, $C\underline{H}_2O$), 7.1—7.5 (14H, m, 2×Ph-H, Ar-H), 7.92 (1H, br s, Ar-N$\underline{H}$). ^{13}C-NMR: 24.6 (C4), 29.4 (–$\underline{C}H_3$), 48.3 (C3), 55.4 (C1), 57.2 ($O\underline{C}H_3$), 69.4 ($\underline{C}H_2O$), 84.6 ($\underline{C}$–CF_3), 108.7 (C4b), 110.9 (C8), 118.3 (C6), 119.6 (C5), 122.0 (C7), 126.3 ($2\times Ph\underline{C}H$), 127.0 (C4a), 127.1 ($Ph\underline{C}H$), 127.4 ($2\times Ph\underline{C}H$), 128.1 ($2\times Ph\underline{C}H$), 128.4 ($2\times Ph\underline{C}H$), 129.7 ($Ph\underline{C}H$), 132.2 ($Ph\underline{C}$), 135.9 ($Ph\underline{C}$), 137.4 (C9a), 146.1 (C8a), 166.4 (O–$\underline{C}$O). LR-EI-MS: *m/z* 508 (M$^+$), 58 (base peak). HR-EI-MS: Calcd for $C_{29}H_{27}N_2O_3F_3$: 508.1974. Found: 508.2011.

Epimerization Reaction of 4 and 5 under Acidic Condition: General Procedure **4** or **5** (50 mg, 0.14 mmol) in TFA (5 ml) was stirred at room temperature at the appropriate time (see Table 3). The ^{1}H-NMR spectrum of the mixture was measured. The ratios of **5**/**4** were calculated from the intensities of the C-3 H signals of the products. Optical rotations of **4** and **5** were measured after column chromatographic purification. **4a**: $[\alpha]_D$ −55.8° (c=1.0 in MeOH). **4b**: $[\alpha]_D$ −44.5° (c=0.5 in MeOH). **4c**: $[\alpha]_D$ −51.0°

(c=0.5 in MeOH). **5a**: $[\alpha]_D$ −12.5° (c=0.9 in MeOH). **5b**: $[\alpha]_D$ −14.0° (c=1.0 in MeOH). **5c**: $[\alpha]_D$ −14.9° (c=1.0 in MeOH).

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