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 (1R,3S)-Diastereomers into Their (1S,3S)-Counterparts by Scission of the C(1)–N(2) Bond

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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 (1S,3S)-1-aryl-3-isopropoxycarbonyl-1-methyl-1,2,3,4-tetrahydro-β-carbolines (4) and their (1R,3S)-diastereomers (5), of which the diastereomer ratios varied from 1 to 5 depending on the reaction conditions. The (1R,3S)-diastereomers (5) are thermodynamically more stable than their (1S,3S)-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 diastereoselectivity 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 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, 1H- and 13C-NMR, [α]D). In the 1H-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 1H-NMR spectrum of trans-diastereomer (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-
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 [α]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-

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

<table>
<thead>
<tr>
<th>Run</th>
<th>Ketones (2)</th>
<th>Acids</th>
<th>Conditions</th>
<th>Yields (%) of β-carbolines (THbCs) Ratio of 4/5a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R</td>
<td>Temp (°C)</td>
<td>Time (h)</td>
<td>4 (1S,3S)</td>
</tr>
<tr>
<td>1</td>
<td>2a H</td>
<td>70</td>
<td>1</td>
<td>4a 10</td>
</tr>
<tr>
<td>2</td>
<td>2a H</td>
<td>rt</td>
<td>1</td>
<td>4a 31</td>
</tr>
<tr>
<td>3</td>
<td>2a H</td>
<td>rt</td>
<td>18</td>
<td>4a 14</td>
</tr>
<tr>
<td>4</td>
<td>2a H</td>
<td>HCOOH</td>
<td>70</td>
<td>18</td>
</tr>
<tr>
<td>5</td>
<td>2a H</td>
<td>HCOOH</td>
<td>rt</td>
<td>18</td>
</tr>
<tr>
<td>6</td>
<td>2b Cl</td>
<td>TFA</td>
<td>70</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>2b Cl</td>
<td>TFA</td>
<td>rt</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>2b Cl</td>
<td>TFA</td>
<td>rt</td>
<td>18</td>
</tr>
<tr>
<td>9</td>
<td>2b Cl</td>
<td>HCOOH</td>
<td>70</td>
<td>18</td>
</tr>
<tr>
<td>10</td>
<td>2b Cl</td>
<td>HCOOH</td>
<td>rt</td>
<td>18</td>
</tr>
<tr>
<td>11</td>
<td>2c OCH3</td>
<td>TFA</td>
<td>70</td>
<td>1</td>
</tr>
<tr>
<td>12</td>
<td>2c OCH3</td>
<td>TFA</td>
<td>rt</td>
<td>1</td>
</tr>
<tr>
<td>13</td>
<td>2c OCH3</td>
<td>TEA</td>
<td>rt</td>
<td>18</td>
</tr>
<tr>
<td>14</td>
<td>2c OCH3</td>
<td>HCOOH</td>
<td>70</td>
<td>18</td>
</tr>
<tr>
<td>15</td>
<td>2c OCH3</td>
<td>HCOOH</td>
<td>rt</td>
<td>18</td>
</tr>
</tbody>
</table>

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

Table 2. 1H- and 13C-NMR Signals (C1 and C3) and [α]D Values of 4 and 5

<table>
<thead>
<tr>
<th>THβCs</th>
<th>R</th>
<th>1H-NMR (δ)</th>
<th>13C-NMR (ppm)</th>
<th>[α]D (c) in MeOH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>C1-CH3</td>
<td>C3-H (J, Hz)</td>
<td>C1</td>
</tr>
<tr>
<td>4a</td>
<td>H</td>
<td>1.92</td>
<td>4.00 (4, 11)</td>
<td>57.0</td>
</tr>
<tr>
<td>4b</td>
<td>Cl</td>
<td>1.90</td>
<td>3.99 (4, 11)</td>
<td>56.7</td>
</tr>
<tr>
<td>4c</td>
<td>OCH3</td>
<td>1.89</td>
<td>3.99 (4, 11)</td>
<td>56.5</td>
</tr>
<tr>
<td>5a</td>
<td>H</td>
<td>1.86</td>
<td>3.50 (5, 11)</td>
<td>57.0</td>
</tr>
<tr>
<td>5b</td>
<td>Cl</td>
<td>1.82</td>
<td>3.45 (5, 11)</td>
<td>56.6</td>
</tr>
<tr>
<td>5c</td>
<td>OCH3</td>
<td>1.84</td>
<td>3.50 (5, 11)</td>
<td>56.5</td>
</tr>
</tbody>
</table>
ethanone (2c) were readily determined by their analogy in the $^1$H- and $^1$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%) ($[\alpha]_D^{19} + 52.7^\circ$) and ent-5a (38%) ($[\alpha]_D^{19} + 9.9^\circ$). Their $^1$H- and $^1$C-NMR signals were identical with those of 4a and 5a, but the specific optical rotations were opposite in sign ($\Delta[\alpha]_D = -53.3^\circ$) and ($\Delta[\alpha]_D = -10.0^\circ$).

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 stereoechemistry C-1 and C-3 chiral centers, were assigned to be (1S,3S) and (1R,3S)-isopropoxycarbonyl-3-methyl-1-phenyl-TH$\beta$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 diastereoselectivity, while the reaction under milder conditions showed high diastereoselectivity. For example, the ratio of 5a/4a in the reaction of 2a with HCOOH at 70°C for 18 h is 1:2 (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$\beta$Cs (4) and (5)$^a$

<table>
<thead>
<tr>
<th>Run</th>
<th>TH$\beta$Cs</th>
<th>R</th>
<th>Conditions</th>
<th>Ratio of 5:4$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4a</td>
<td>H</td>
<td>rt 1 h</td>
<td>1.4</td>
</tr>
<tr>
<td>2</td>
<td>4a</td>
<td>H</td>
<td>rt 3 h</td>
<td>3.0</td>
</tr>
<tr>
<td>3</td>
<td>4b</td>
<td>Cl</td>
<td>rt 1 h</td>
<td>0.8</td>
</tr>
<tr>
<td>4</td>
<td>4b</td>
<td>Cl</td>
<td>rt 3 h</td>
<td>3.0</td>
</tr>
<tr>
<td>5</td>
<td>4c</td>
<td>OCH$_3$</td>
<td>rt 20 min</td>
<td>3.0</td>
</tr>
<tr>
<td>6</td>
<td>4c</td>
<td>OCH$_3$</td>
<td>rt 1 h</td>
<td>3.0</td>
</tr>
<tr>
<td>7</td>
<td>5a</td>
<td>H</td>
<td>rt 3 h</td>
<td>4.0</td>
</tr>
<tr>
<td>8</td>
<td>5b</td>
<td>Cl</td>
<td>rt 3 h</td>
<td>10.0</td>
</tr>
<tr>
<td>9</td>
<td>5b</td>
<td>Cl</td>
<td>rt 18 h</td>
<td>4.5</td>
</tr>
<tr>
<td>10</td>
<td>5e</td>
<td>OCH$_3$</td>
<td>rt 20 min</td>
<td>4.0</td>
</tr>
</tbody>
</table>

*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 Conformer of 4a and 5a Optimized by AM1](https://example.com/figures/f1.png)

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 1H-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 ($\Delta H_f =$
The facts described above, in turn, supported 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–Spangler reaction, and b) the C(1)–N(2) bond fission-recombination. The mechanism of the retro-Pictet–Spangler 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 results described above, in turn, supported the conclusion obtained from the isomerization experiments. Unless otherwise noted, the following procedures were adopted. Melting point were taken 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 F254 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 Na2SO4, and concentrated in vacuo to dryness.

The Pictet–Spangler Reaction of 4-L-Tryptophan methyl ester with Ace- tophenone (2a): Typical procedure 1-L-Tryptophan methyl ester hydrochloride (1) (1.2 g, 4.59 mmol) in H2O (50 ml) was basified with 10% K2CO3 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-iPr)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 SiO2 column (MeOH) to remove TiO2. The eluent was concentrated in vacuo (ca. 30 ml) and the residue was neutralized with 10% NaOH solution and extracted with CHCl3.

After removal of the solvent of the extract in vacuo, the residue was purified by column chromatography over SiO2 (benzenes-ace-tone=30:1) to give 4a (111 mg, 10%) and 5a (604 mg, 45%).

(1S,3S)-3-Isopropoxy carbonyl-1-methyl-1-phenyl-1,2,3,4-tetrahydro-β-carboline (4a): Colorless prisms recrystallized from Et2O-hexane, mp 185—187 °C. IR: 3384, 3342, 2979, 2935, 1718. 1H-NMR: 1.30 (3H, d, J=7 Hz, CH(CH3)2), 1.32 (3H, d, J=7 Hz, CH(CH3)2), 1.92 (3H, s, CH3), 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). HR-EI-MS: Calcd for C22H24N2O2: 348.1838. Found: 348.1863.

(1R,3S)-3-Isopropoxy carbonyl-1-methyl-1-phenyl-1,2,3,4-tetrahydro-β-carboline (5a): Colorless needles recrystallized from Et2O-hexane, mp 175—176 °C. IR: 3369, 2979, 1724, 1654. UV: 278.5 (8500). 1H-NMR: 1.24 (3H, d, J=6 Hz, CH(CH3)2), 1.27 (3H, d, J=6 Hz, CH(CH3)2), 1.86 (3H, s, CH3), 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, CH(=CH)2), 7.1—7.9 (10H, m, Ph-H, Ar-H). HR-EI-MS: 218.2 (2CH2CH3), 257.7 (CH3), 264.4 (C4), 53.3 (C3), 57.0 (C1), 68.6 (CH(=CH)2), 108.4 (C4a), 110.9 (C9a), 118.3 (C6), 119.5 (C5), 121.9 (C7), 126.9 (C4b), 127.0 (2CH2Ph), 127.8 (PhC-H), 130.0 (PhC-H), 130.4 (PhC-H), 130.9 (C13a), 145.3 (C8a), 172.9 (COO).

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%).

(1S,3S)-1-(4-Chlorophenyl)-3-isopropoxy carbonyl-1-methyl-1,2,3,4-tetrahydro-β-carboline (4b): Colorless needles recrystallized from Et2O-hexane, mp 195—197 °C. IR: 3384, 3342, 2979, 2935, 1718. 1H-NMR: 1.30 (3H, d, J=6 Hz, CH(CH3)2), 1.32 (3H, d, J=6 Hz, CH(CH3)2), 1.90 (3H, s, CH3), 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, CH(=CH)2), 7.1—7.6 (10H, m, Ph-H, Ar-H). HR-EI-MS: Calcd for C22H24N2O2Cl: 388.1893. Found: 388.1817.
6.7 (m, Ar-H), 2.85 (1H, dd, J=5, 11 Hz, 3-H), 3.08 (1H, m, 3-H), 3.45 (1H, d, J=11, 15 Hz, 4-H), 3.50 (1H, dd, J=5, 11 Hz, 3-H), 3.56 (1H, s, CH), 3.79 (3H, s, OCH3), 3.99 (1H, dd, J=5, 11 Hz, 3-H), 4.06 (1H, dd, J=5, 11 Hz, 3-H), 4.27 (1H, d, J=3, 10 Hz, 5-H), 4.32 (1H, dd, J=5, 11 Hz, 3-H), 4.45 (1H, d, J=3, 10 Hz, 5-H), 7.1—7.7 (9H, m, Ar-H, Ph-H). 13C-NMR: 21.8 (2CH3), 29.8 (C3), 34.4 (C2), 55.3 (OCO), 56.5 (C1), 68.5 (CH3), 108.0 (C4a), 110.9 (C8), 113.8 (2C6), 115.0 (C11), 115.9 (C12), 124.7 (C16b), 127.3 (C16a), 128.3 (2C13), 129.1 (C13), 131.2 (C11a), 135.9 (PhC6), 137.2 (C15), 139.3 (C19a), 159.0 (PhC10), 172.9 (COO). LR-EM: m/z 382 (M+1), 378 (base peak). HR-EI-MS: Calcd for C23H26N2O3: 378.1944. Found: 378.1979.

Table 1 (Run 11) gave 4c (183 mg, 13%) and 4d (144 mg, 92%) as a colorless gum. IR: 3397, 3291, 2969, 2925. 1H-NMR: 1.73 (3H, s, CH3), 2.80 (1H, d, J=5, 11 Hz, 3-H), 3.08 (1H, dd, J=5, 11 Hz, 3-H), 3.45 (1H, d, J=5, 11 Hz, 3-H), 3.50 (1H, dd, J=5, 11 Hz, 3-H), 3.56 (1H, s, CH), 3.79 (3H, s, OCH3), 3.99 (1H, dd, J=5, 11 Hz, 3-H), 4.06 (1H, dd, J=5, 11 Hz, 3-H), 4.27 (1H, d, J=3, 10 Hz, 5-H), 4.32 (1H, dd, J=5, 11 Hz, 3-H), 4.45 (1H, d, J=3, 10 Hz, 5-H), 7.1—7.7 (9H, m, Ar-H, Ph-H). 13C-NMR: 24.7 (C4), 29.8 (C3), 55.4 (OCO), 57.3 (C1), 66.0 (C10), 109.3 (C4a), 110.9 (C8), 111.6 (C17), 120.2 (C15), 122.8 (2C13), 125.9 (C13), 135.9 (PhC6), 137.2 (C15), 139.3 (C19a), 159.0 (PhC10), 172.9 (COO). LR-EM: m/z 382 (M+1), 378 (base peak). HR-EI-MS: Calcd for C23H26N2O3: 378.1944. Found: 378.1979.

Typical Procedure: A solution of 2a (54 mg, 0.37 mmol) in CCl4 (15 ml) was basified with 10% K2CO3 solution and extracted with AcOEt. After removal of the solvent in vacuo, the residue was purified by column chromatography over SiO2 (AcOEt–hexane 1:1) to give 1a (54 mg, 92%) as a colorless gum.

Synthesis of (I.S,3S)-3-Isopropoxycarbonyl-1-methyl-1-phenyl-1,2,3,4-tetrahydrol-carboline (8): Typical Procedure 1 A solution of 6 (42 mg, 0.144 mmol), pyridine (1.7 ml), DMAF (7 mg) and (-)-MTPA-Cl (90 mg, 0.360 mmol) in CCl4 (3 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 CHCl3. After removal of the solvent, the residue was purified by column chromatography over SiO2 (AcOEt–hexane 1:1) to give 7 (48 mg, 66%) as a pale yellow gum. IR: 3058, 2965, 2921, 1745. 1H-NMR: 1.69 (3H, s, CH3), 2.57 (1H, dd, J=11, 15 Hz, 4-H), 2.73 (1H, dd, J=5, 11 Hz, 4-H), 3.1—3.2 (1H, m, 3-H), 3.46 (1H, d, J=11, 15 Hz, 4-H), 4.32 (1H, dd, J=7, J=11 Hz, CH2O), 4.45 (1H, d, J=3, 10 Hz, CH2O), 7.1—7.6 (8H, m, Ph-H). Water was added to the reaction mixture and the mixture was extracted with CHCl3. After removal of the solvent, the residue was purified by column chromatography over SiO2 (AcOEt–hexane 1:1) to give 8 (42 mg, 83%) as a colorless gum.

Reduction of ent-5a with LiAlH4 Reduction of ent-5a (200 mg, 0.575 mmol) with LiAlH4 (22 mg, 0.575 mmol) and purification by column chromatography over SiO2 (benzene–acetone 3:1) gave (1R,3S)-3-hydroxy-1-methyl-1-phenyl-1,2,3,4-tetrahydrol-carboline (6) (140 mg, 83%) as a colorless gum. IR, 1H- and 13C-NMR were identical with those of 6. 1H-NMR: 1.60 (3H, s, CH3), 2.70 (1H, dd, J=5, 11 Hz, 4-H), 2.79 (1H, dd, J=5, 11 Hz, 4-H), 3.02 (1H, m, 3-H), 3.08 (1H, dd, J=5, 11 Hz, 4-H), 3.82 (1H, d, J=11, 15 Hz, 4-H), 3.98 (1H, d, J=3, 10 Hz, 5-H), 4.06 (1H, dd, J=3, 10 Hz, 5-H), 7.1—7.6 (8H, m, Ph-H). 13C-NMR: 24.7 (C4), 29.8 (C3), 55.4 (OCO), 57.3 (C1), 66.0 (C10), 109.3 (C4a), 110.9 (C8), 111.6 (C17), 120.2 (C15), 122.8 (2C13), 125.9 (C13), 135.9 (PhC6), 137.2 (C15), 139.3 (C19a), 159.0 (PhC10), 172.9 (COO). LR-EM: m/z 308 (M+1), 284 (base peak). HR-EI-MS: Calcd for C17H19NO2F: 308.1580. Found: 308.1797. Reducition of ent-5a with LiAlH4: Typical Procedure (25 mg, 0.07 mmol) was dissolved in 10 ml of THF. After removal of the solvent in vacuo, the residue was mixed with (50 ml) was basified with 10% K2CO3 solution and extracted with AcOEt. After removal of the solvent in vacuo, the residue was purified by column chromatography over SiO2 (AcOEt–hexane 1:1) as a pale yellow gum.

Eimerization Reaction of 4 and 5 under Acidic Condition: General Procedure A solution of 4 (50 mg, 0.12 mmol) in 10 ml of TFA (5 ml) was stirred at room temperature at the appropriate time (see Table 3). The 1H-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: [α]29D +55.8° (c=1.0 in MeOH). 4b: [α]29D +44.5° (c=0.5 in MeOH).

4. [α]29D +51.0°

2a

2a

2a

2a

2a

2a

2a

(c=0.5 in MeOH). 5a: $[\alpha]_D^{20} = -12.5^\circ$ (c=0.9 in MeOH). 5b: $[\alpha]_D^{20} = -14.0^\circ$ (c=1.0 in MeOH). 5c: $[\alpha]_D^{20} = -14.9^\circ$ (c=1.0 in MeOH).

References and Notes