CHIRAL AUXILIARY APPROACH TO THE ASYMMETRIC PICTET-SPENGLER REACTION OF TRYPTAMINES

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Abstract- The diastereoselective Pictet-Spengler reaction of chiral tryptamines bearing an α-naphthylethyl auxiliary group was investigated. In the presence of trifluoroacetic acid as a catalyst, the Pictet-Spengler reaction of various aldehydes gave the corresponding tetrahydro-β-carbolines at a diastereoselectivity of up to 93:7.

The transformation of arylethylamines and aldehydes into tetrahydroisoquinolines or tetrahydro-β-carbolines is well known as the Pictet-Spengler (PS) reaction.[1] Since numerous natural compounds containing these heterocycles have been isolated and have shown interesting biological activities, the PS reaction is recognized to be very important in both organic chemistry and medicinal chemistry. Since many of these alkaloids are optically active, the development of a stereoselective PS reaction has been actively investigated.[2] Although the detailed mechanism of the PS reaction is still unclear, a new stereogenic center results from nucleophilic attack of the indole nucleus to an iminium functionality, as shown in Figure 1.[3] Hence, generation of a chiral iminium intermediate is one of the key points in the development of an asymmetric PS reaction. Although chiral auxiliary groups are often investigated in stereoselective reactions, to our surprise, the use of chiral auxiliary groups for this PS cyclization has received little attention.[4] Recently, we developed a reagent-controlled enantioselective PS reaction.[2a,b] We also reported the use of an α-phenylethyl auxiliary in the asymmetric PS reaction, and observed up to 72% de .[2c] In this paper, we report the diastereoselective PS reaction using an α-naphthylethyl chiral

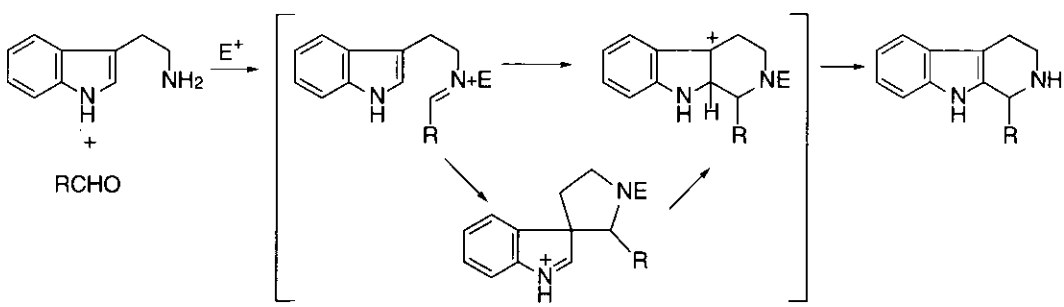
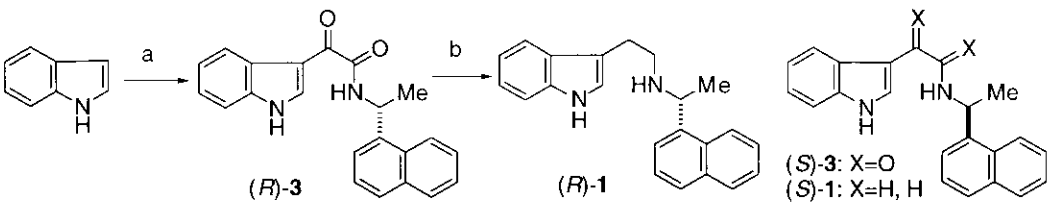


Figure 1. Mechanism of Pictet-Spengler reaction.



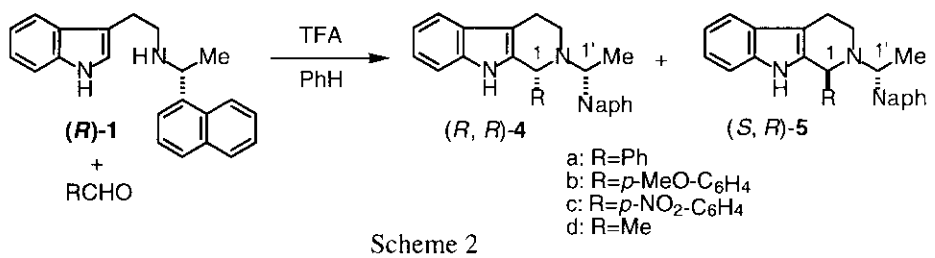
Reagents and conditions: a) i) $(COCl)_2$, Et_2O, rt, 1.5 h; ii) (*R*)-α-Naphthylethylamine ((*R*)-**2**), Et_3N, THF, 0 °C, 3 h, 96 %, b) $LiAlH_4$, $AlCl_3$, THF, 0 °C, 2 h then rt, 5 h, 96 %.

Scheme 1

auxiliary.

The chiral tryptamine ((*R*)-**1**) was prepared from indole and (*R*)-α-naphthylethylamine ((*R*)-**2**), according to the method for an α-phenethyl analog (Scheme 1).[2c] Thus, indole was first treated with oxalyl chloride, and the resulting indoleoxalyl chloride was condensed with (*R*)-**2** to give amide ((*R*)-**3**). The amide ((*R*)-**3**) was reduced with $LiAlH_4$-$AlCl_3$ to furnish (*R*)-**1** in 92% yield from indole. The enantiomeric tryptamine ((*S*)-**1**) was also synthesized from indole and (*S*)-α-naphthylethylamine ((*S*)-**2**), *via* (*S*)-**3**, in 70% overall yield.

With chiral tryptamines (**1**) in hand, we next examined the asymmetric PS reaction under various conditions. The results are summarized in the Table (Scheme 2). When a mixture of (*R*)-**1** and benzaldehyde in benzene was stirred for 7 d at room temperature or for 5 d at 50°C in the presence of 3 equivalents of trifluoroacetic acid (TFA), no β-carboline was obtained and (*R*)-**1** was recovered almost quantitatively in both reactions (Entries 1 and 2). When the reaction was carried out in refluxing benzene for 4 d, the expected tetrahydro-β-carbolines ((*R,R*)-**4a**) and ((*S,R*)-**5a**) were obtained as a mixture of diastereomers in 45% yield with a diastereomer ratio of (*R,R*)-**4a** : (*S,R*)-**5a** = 93:7 (Entry 3). The diastereomer ratio was determined by means of ^{1}H-NMR spectra. We next examined the reaction conditions to improve the chemical yield as well as the diastereoselectivity. By increasing the amount of TFA to 5 equivalents and that of benzaldehyde to 3 equivalents, the chemical yield of β-carbolines (**4a+5a**) was improved to 66% after refluxing for 2 days, without a loss of diastereoselectivity (Entry 4). Further improvement to 72% yield with 84% de was achieved with the use of 10 equivalents of TFA and 5 equivalents of benzaldehyde, as shown in Entry 5. With a solvent with a higher boiling point (toluene), the reaction proceeded within 1 day and the β-carbolines (**4a+5a**) were isolated in 90% yield. However, diastereoselectivity decreased to 71:29 (Entry 6). We then examined this reaction with other aldehydes. The reaction with *p*-anisaldehyde was highly diastereoselective (**4b**: **5b** = 91: 9), but was very slow and β-carbolines (**4b+5b**) were obtained in only 9% yield after 2 days (Entry 7). On the other hand, the reactivity of *p*-nitrobenzaldehyde toward tryptamine (*R*)-**1** was almost the same as that of benzaldehyde, and the yield of β-carbolines (**4c+5c**) was 58% with 60% de (Entry 8). Aliphatic acetaldehyde also reacted with (*R*)-**1** to give β-carbolines (**4d+5d**) in 33% yield with moderate diastereoselectivity (Entry 10). With bulky aldehydes, such as 1-naphthylaldehyde and isovaleraldehyde, only unidentified products were isolated, although tryptamine (**1**) had completely disappeared by a TLC analysis, and neither β-carbolines nor tryptamine ((*R*)-**1**) was isolated (Entries 9 and 11). The reaction of enantiomeric (*S*)-**1** with benzaldehyde also gave β-carbolines ((*S,S*)-**4a**) and ((*R,S*)-**5a**) in 62% yield with diastereomer ratio



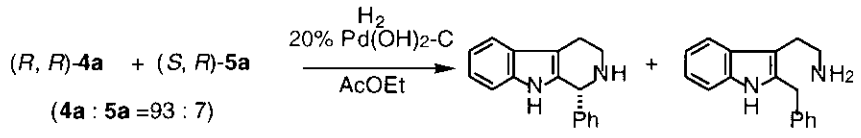
Scheme 2

Table. Diastereoselective Pictet-Spengler Reaction of (*R*)-**1**

Entry	RCHO (mol equiv)	TFA (mol equiv)	temp	time	**4** + **5**	yield (%)	**4** : **5**[a]
1	PhCHO (5.0)	3.0	rt	7 d		NR	---
2	PhCHO (5.0)	3.0	50 °C	5 d		NR	---
3	PhCHO (1.1)	1.5	reflux	4 d	**a**	45	93 : 7
4	PhCHO (3.0)	5.0	reflux	2 d	**a**	66	91 : 9
5	PhCHO (10.0)	5.0	reflux	1 d	**a**	72	92 : 8
6	PhCHO (3.0)	5.0	reflux[b]	1 d	**a**	90	71 : 29
7	*p*-MeO-C_6H_4CHO (3.0)	5.0	reflux	2 d	**b**	9	91 : 9
8	*p*-NO_2-C_6H_4CHO (3.0)	5.0	reflux	2 d	**c**	58	80 : 20
9	α-Naphthyl-CHO (3.0)	5.0	reflux	2 d		–[c]	
10	MeCHO (3.0)	5.0	reflux	2 d	**d**	33	70 : 30
11	*i*BuCHO (3.0)	5.0	reflux	2 d		–[c]	
12	PhCHO (3.0)	5.0	reflux	2 d	**a**[d]	62	87 : 13

a) Determined by ^{1}H-NMR, b) Toluene was used as a solvent, c) unidentified products, d) (*S*)-**1** was used.

4a:**5a**=87:13 (Entry 12). To confirm the stereochemistry of **4** and **5**, the chiral auxiliary was removed by hydrogenolysis. Thus, a mixture of (*R,R*)-**4a** and (*S,R*)-**5a** was stirred under a hydrogen atmosphere in the presence of 20% $Pd(OH)_2$-C, and 1-phenyltetrahydro-β-carboline (**6**) was isolated in 14% yield, along with over-reduced 2-benzyltryptamine (**7**) in 32% yield (Scheme 3). Based on a comparison of the specific rotation of **6** ($[\alpha]_D^{21}$ +10.6° (c 0.50, EtOH)) with that for (*S*)-**6** ($[\alpha]_D^{21}$ -14.6° (c 0.50, EtOH)),[5] β-carboline (**6**) was determined to be enriched with the 1*R*-enantiomer. Thus, the stereochemistry of the major isomer (**4a**) from (*R*)-**1** was determined to be *1R,1'R* while that of the minor isomer (**5a**) was 1*S*,1'*R*.[6]



Scheme 3

Further investigation of the asymmetric Pictet-Spengler reaction as well as its application to natural product synthesis is currently underway.

EXPERIMENTAL SECTION

Melting points were determined with Yamato MP-1 and Yanagimoto micro melting point instruments and are uncorrected. IR spectra (υ in cm^{-1}) were recorded with Hitachi 260-10 and JASCO IR-350 spectrophotometers. Unless otherwise noted, IR spectra refer to KBr disks. MS spectra were recorded on a JEOL HX-110 mass spectrometer. Proton (400 MHz) and carbon (100 MHz) NMR (^{1}H- and ^{13}C-NMR) spectra were recorded on a JEOL JNM-GSX-400A apparatus. NMR spectra were measured in $CDCl_3$, unless otherwise noted, and chemical shifts were recorded in δ values (ppm) relative to Me_4Si as an internal standard. Optical rotations were recorded with a JASCO DIP-140 polarimeter. Microanalyses were performed on a Perkin Elmer 240 C, H, N analyzer.

(*R*)-N_b-α-Naphthylethyl Indole-3-glyoxylamide ((*R*)-3)

To a stirred solution of indole (5.91 g, 51 mmol) in ether (150 mL) was added oxalyl chloride (6.3 mL, 66 mmol), and the mixture was stirred for 1.5 h at rt. The resulting yellow solid, crude indoleoxalyl chloride, was collected by filtration and washed with ether. The yellow solid was then dissolved in THF (150 mL), and (*R*)-(-)-α-naphthylethylamine ((*R*)-**2**) (9.8 mL, 60 mmol) and Et_3N (8.4 mL, 60 mmol) were added to the reaction mixture at 0°C. After stirring for 3 h at 0°C, H_2O (70 mL) was added and the organic layer was separated and washed with 10% HCl, saturated $NaHCO_3$, and brine, and dried over Na_2SO_4. Evaporation of the solvent gave a solid yellow residue, which was purified by crystallization from MeOH and by silica gel column chromatography to give (*R*)-**3** (total 16.71 g, 96%) as colorless prisms. mp 199.0~199.5°C(MeOH). $[\alpha]_D^{23}$ -64.7° (c 1.00, $CHCl_3$). IR 3250, 1655, 1600, 1500, 1230, 1140, 770 cm^{-1}; ^{1}H-NMR δ: 1.75 (3H, d, *J*=7.0 Hz, Me), 5.96 (1H, q, *J*=7.2 Hz, C<u>H</u>Me), 7.25~7.36 (3H, m, Ar), 7.44~7.57 (4H, m, Ar), 7.79 (1H, d, *J*=8.1 Hz, Ar), 7.86 (1H, d, *J*=8.7 Hz, Ar), 7.97 (1H, d, *J*=8.3 Hz, Ar), 8.12 (1H, d, *J*=8.3 Hz, Ar), 8.38 (1H, d, *J*=7.3 Hz, Ar), 9.05 (1H, d, *J*=3.4 Hz, CONH), 9.17 (1H, s, N_a-H); LRFABMS m/z(%) 343 (MH^+, 21), 307 (42), 154(100). Anal. Calcd for $C_{22}H_{18}N_2O_2$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.08; H, 5.23; N, 8.09.

(*S*)-**3** was prepared as above from indole and (*S*)-(+)-α-naphthylethylamine ((*S*)-**2**) in 88% yield. mp 199.0~199.5°C (MeOH). $[\alpha]_D^{21}$ +65.4° (c 1.00, $CHCl_3$).

(*R*)-*N*-(β-3-Indolylethyl)-α-naphthylethylamine ((*R*)-1)

To a suspension of $LiAlH_4$ (1.71 g, 45 mmol) in THF (130 mL) was added $AlCl_3$ (5.85 g, 44 mmol) portionwise at 0°C. After the mixture was stirred for 0.5 h at 0°C, (*R*)-**3** (3.00 g, 9 mmol) in THF (20 mL) was added dropwise at 0°C. After stirring for 2 h at 0°C, and then for 5 h at rt, the reaction was quenched with 20% NaOH at 0°C. The precipitate was filtered and washed with CH_2Cl_2, and the combined filtrate was washed with brine and dried over Na_2SO_4. The solvent was evaporated and the residue was chromatographed on Al_2O_3 (Et_2O:hexane=1:3) to give (*R*)-**1** (2.65 g, 96%) as a yellow gummy oil. $[\alpha]_D^{23}$ +45.5° (c 1.00, $CHCl_3$). IR(neat) 3400, 1600, 1500, 1450, 1230, 1110, 780, 740 cm^{-1}; ^{1}H-NMR δ: 1.46 (3H, d, *J*=6.6 Hz, Me), 1.63 (1H, br s, N_b-H), 2.93~3.01 (4H, m, 2xCH_2), 4.63 (1H, q, *J*=6.6 Hz, C<u>H</u>Me), 6.99 (1H, s, Ar), 7.08 (1H, t, *J*=7.0 Hz, Ar), 7.21 (1H, t, *J*=7.3 Hz,

Ar), 7.34~7.46 (4H, m, Ar), 7.53~7.58 (2H, m, Ar), 7.71 (1H, d, *J*=7.8 Hz, Ar), 7.84 (1H, d, *J*=7.6 Hz, Ar), 7.95 (1H, br s, NH), 8.07 (1H, d, *J*=7.6 Hz, Ar); LRFABMS m/z(%) 315 (MH^+, 74), 155 (100).

(*S*)-**1** was prepared as above from (*S*)-**3** in 84% yield. $[\alpha]_D^{23}$ -44.7° (c 0.99, $CHCl_3$).

Typical procedure for the Pictet-Spengler reaction: reaction of (*R*)-1 with benzaldehyde (Entry 5)

To a stirred solution of (*R*)-**1** (315 mg, 1 mmol) and benzaldehyde (1.05 mL, 10 mmol) in dry benzene (80 mL) was added trifluoroacetic acid (0.40 mL, 5 mmol). The reaction mixture was refluxed for 1 d under an argon atmosphere. The reaction mixture was cooled to rt and made alkaline with 15% aqueous NaOH. The organic layer was separated, dried over Na_2SO_4, and evaporated. Chromatography of the residue on silica gel gave a mixture of **4a** and **5a** (290 mg, 72%). The ^{1}H-NMR spectrum was taken in $CDCl_3$, and the diastereomer ratio was calculated by integrating C-1 protons; **4a** δ 4.79, **5a** δ 5.15.

2[(*R*)-α-Naphthylethyl]-1-(*R*)-phenyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (4a) and 2[(*R*)-α-Naphthylethyl]-1-(*S*)-phenyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (5a): Yellow amorphous solid. $[\alpha]_D^{21}$ +37.8° (c 0.96, $CHCl_3$). IR 3400, 2960, 1720, 1450, 1260, 1100, 1030, 800, 740 cm^{-1}; ^{1}H-NMR δ: 1.55 (3H, d, *J*=6.6 Hz, -CH_3), 2.56 (1H, ddd, *J*=4.5, 4.7, 15.5 Hz, C_4-H_a), 2.91 (1H, ddd, *J*=5.8, 8.7, 16.5 Hz, C_4-H_b), 3.10 (1H, ddd, *J*=4.9, 8.5, 13.4 Hz, C_3-H_a), 3.20 (1H, ddd, *J*=4.7, 4.7, 13.4 Hz, C_3-H_b), 4.68 (1H, q, *J*=6.6 Hz, -C<u>H</u>(Naph)Me), 4.79 (s, C_1-H of **4a**), 5.15 (s, C_1-H of **5a**), 7.05-7.51 (13H, m, Ar), 7.67-7.89 (4H, m, Ar); LRFABMS: 403 (MH^+, 17), 155 (100).

2[(*R*)-α-Naphthylethyl]-1-(*R*)-(4-methoxyphenyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (4b) and 2[(*R*)-α-Naphthylethyl]-1-(*S*)-(4-methoxyphenyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (5b): Yellow amorphous solid. ^{1}H-NMR δ: 1.61 (3H, d, *J*=6.6 Hz, -CH_3), 2.61 (1H, td, *J*=4.7, 15.6 Hz, C_4-H_a), 2.94 (1H, m, C_4-H_b), 3.10-3.30 (2H, m, C_3-H_2), 3.75 (3H, s,.OCH_3), 4.73 (1H, q, *J*=6.6 Hz, -C<u>H</u>(Naph)Me), 4.81 (s, C_1-H of **4b**), 5.16 (s, C_1-H of **5b**), 6.78 (2H, d, *J*=8.5 Hz, Ar), 7.02 (2H, d, *J*=8.5 Hz, Ar), 7.10-7.60 (7H, m, Ar), 7.70-7.85 (4H, m, Ar), 7.97 (1H, br s, NH); LRFABMS: 433 (MH^+), 155 (100). HRFABMS: Calcd for $C_{30}H_{28}N_2O$+H: 433.2282. Found: 433.2285.

2[(*R*)-α-Naphthylethyl]-1-(*R*)-(4-nitrophenyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (4c): Yellow caramel. ^{1}H-NMR δ: 1.62 (3H, d, *J*=6.6 Hz, -CH_3), 2.65 (1H, m, C_4-H_a), 3.06 (2H, m, C_4-H_b and C_3-H_a), 3.42 (1H, m, C_3-H_b), 4.69 (1H, q, *J*=6.6 Hz, -C<u>H</u>(Naph)Me), 4.73 (1H, s, C_1-H), 7.05-8.05 (16H, m, Ar and NH); ^{13}C-NMR δ: 17.55 (C4), 19.90 (Me), 39.99 (C3), 55.05 (CH), 58.46 (C1), 110.35 (Ar), 110.96 (Ar), 118.38 (Ar), 119.61 (Ar), 122.02 (Ar), 123.04 (Ar), 123.90 (Ar), 125.57 (Ar), 127.05 (Ar), 127.89 (Ar), 128.86 (Ar), 129.55 (Ar), 131.04 (Ar), 131.58 (Ar), 134.08 (Ar), 136.01 (Ar), 141.21 (Ar), 146.91 (Ar), 149.65 (Ar).

2[(*R*)-α-Naphthylethyl]-1-(*S*)-(4-nitrophenyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (5c): Yellow caramel. ^{1}H-NMR δ: 1.62 (3H, d, *J*=6.6 Hz, -CH_3), 2.62 (1H, m, C_4-H_a), 2.89-3.02 (3H, m, C_4-H_b and C_3-H_2), 4.75 (1H, q, *J*=6.6 Hz, -CH(Naph)Me), 5.30 (1H, s, C_1-H), 7.12-8.26 (16H, m, Ar and NH); ^{13}C-NMR δ: 19.54 (C4), 20.87 (Me), 42.59 (C3), 55.69 (CH), 57.05 (C1), 110.48 (Ar), 110.94 (Ar), 118.53 (Ar), 119.68 (Ar), 122.17 (Ar), 123.25 (Ar), 123.78 (Ar), 124.92 (Ar), 125.39 (Ar), 125.45 (Ar), 125.78 (Ar), 127.14 (Ar), 127.68 (Ar), 128.88 (Ar), 129.35 (Ar), 131.57 (Ar), 131.82 (Ar), 134.03 (Ar), 136.27 (Ar), 139.78 (Ar), 147.05 (Ar), 150.24 (Ar).

2[(*R*)-α-Naphthylethyl]-1-(*R*)-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (4d): Yellow caramel. ^{1}H-NMR δ: 1.25 (3H, d, *J*=6.9 Hz, C_1-CH_3), 1.52 (3H, d, *J*=6.6 Hz, -CH_3), 2.51 (1H, dd, *J*=2.9, 15.6 Hz, C_4-H_a), 2.93 (1H, ddd, *J*=4.9, 12.0, 16.1 Hz, C_4-H_b), 3.22 (1H, ddd, *J*=4.4, 11.4, 13.4 Hz, C_3-H_a), 3.40 (1H, dd, *J*=4.4, 14.2 Hz, C_3-H_b), 3.72 (1H, q, *J*=6.9 Hz, C_1-H), 4.64 (1H, q, *J*=6.6 Hz, -CH(Naph)Me), 7.06 (4H, d, *J*=2.9 Hz, Ar), 7.29-7.50 (4H, m, Ar), 7.72-7.83 (3H, m, Ar), 8.02 (1H, br d, *J*=8.1 Hz, Ar); ^{13}C-NMR δ: 18.00, 19.76, 21.08, 40.07, 50.43, 55.26, 107.66, 110.63, 117.91, 119.41, 121.14, 123.74. 124.37, 125.33, 125.52, 125.79, 127.09, 127.25, 128.14; *LRFABMS: 341 (MH$^+$, 17), 155 (100). HRFABMS: Calcd for $C_{24}H_{24}N_2$+H: 341.2020.* Found: 341.1990.

2[(*R*)-α-Naphthylethyl]-1-(*S*)-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (5d): Yellow caramel. ^{1}H-NMR δ: 1.39 (3H, d, *J*=6.8 Hz, C_1-CH_3), 1.54 (3H, d, *J*=6.4 Hz, -CH_3), 2.48 (1H, m, C_4-H_a), 2.85 (1H, m, C_4-H_b), 3.12 (2H, m, C_3-H_2), 4.25 (1H, q, *J*=6.8 Hz, C_1-H), 4.69 (1H, q, *J*=6.6 Hz, -CH(Naph)Me), 7.07-7.88 (11H, m, Ar), 8.57 (1H, br s, Ar); LRFABMS: 341 (MH$^+$, 17), 155 (100). HRFABMS: Calcd for $C_{24}H_{24}N_2$+H: 341.2020. Found: 341.2003.

(*R*)-1-Phenyl-1,2,3,4-tetrahydro-β-carboline ((*R*)-6) and 2-benzyltryptamine (7)

A mixture of β-carbolines (**4a**) and (**5a**) (117 mg, 0.29 mmol, **4a**:**5a**=93:7, obtained from (*R*)-**1**) was dissolved in AcOEt (7 mL) and subjected to catalytic hydrogenation over 20% palladium hydroxide on carbon (35 mg) at rt. After stirring for 25 h, additional catalyst (23 mg) was added and the whole mixture was stirred for an additional 23 h under a hydrogen atmosphere. The catalyst was removed by filtration, and the filtrate was evaporated to give a residue, which was chromatographed on silica gel (AcOEt : MeOH = 3 : 1) to give 1-phenyltetrahydro-β-carboline ((*R*)-**6**) (10 mg, 14 %) and 2-benzyltryptamine (**7**) (23 mg, 32%). (*R*)-**6**: $[\alpha]_D^{21}$ +10.6° (c 0.50, EtOH). This product was spectroscopically identical to known **6**[5] and the absolute configuration was determined by measuring the specific rotation, which indicated *R*.[5] **7**: IR 3353, 2932, 1534, 1493, 1455, 1018, 742 cm^{-1}; ^{1}H-NMR δ: 2.98-3.02 (4H, m, CH_2 x 2), 3.13 (2H, br s, NH_2), 4.12 (2H, s, CH_2Ph), 7.05-7.31 (8H, Ar), 7.55 (1H, m, Ar), 7.78 (1H, br s, NH). *LRFABMS: 251 (MH$^+$), 234 (100).*

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REFERENCES AND NOTES

1) (a) W. M. Whaley and T. R. Govindachari, '*Organic Reactions*', Vol. 6, pp. 151-190, **1951**, John Wiley & Sons; (b) E. D. Cox and J. M. Cook, *Chem. Rev.*, **1995**, *95*, 1797.

2) Recent reports: (a) T. Kawate, H. Yamada, T. Soe, and M. Nakagawa, *Tetrahedron: Asymmetry*, **1996**, *7*, 1249; (b) T. Kawate, H. Yamada, M. Matsumizu, A. Nishida, and M. Nakagawa, *SYNLETT*, **1997**, 761; (c) T. Soe, T. Kawate, N. Fukui, T. Hino, and M. Nakagawa, *Heterocycles*, **1996**, *42*, 347; (d) P. Zhang and J. M. Cook, *Tetrahedron Lett.*, **1995**, *36*, 6999, and references cited therein; (e) H. Waldmann and G. Schmidt, *Tetrahedron*, **1994**, *50*, 11865; (f) P. D. Bailey, M. H. Moore, K. M. Morgan, D. I. Smith, and J. M. Vernon, *Tetrahedron Lett.*, **1994**, *35*, 3587; (g) P. Melnyk, P. Ducrot, and C. Thal, *Tetrahedron*, **1993**, *49*, 8586; (h) J. Liu, M. Nakagawa, K. Ogata, and T. Hino, *Chem. Pharm. Bull.*, **1991**, *39*, 1672, (i) I. M. Piper and D. B. MacLean, *Can. J. Chem.*, **1983**, *61*, 2721; (j) H. Waldmann, G. Schmidt, H. Henke, and M. Burkard, *Angew. Chem., Int. Ed. Engl.*, **1995**, *34*, 2401; (k) G. Schmidt, H. Waldmann, H. Henke, and M. Burkard, *Chem. Eur. J.*, **1996**, *2*, 1566.

3) (a) F. Ungemach and J. M. Cook, *Heterocycles*, **1978**, *9*, 1089; (b) T. Kawate, M. Nakagawa, K. Ogata, and T. Hino, *Heterocycles*, **1992**, *33*, 801.

4) (a) C. Bohlman, R. Bohlman, E. G. Rivera, C. Vogel, M. D. Manandhar, and E. Winterfeldt, *Liebigs Ann. Chem.*, **1985**, 1752; (b) D. L. Comins and M. M. Badawi, *Tetrahedron Lett.*, **1991**, *32*, 2995; R. Amann and D. Spitzner, *Angew. Chem. Int. Ed. Engl.*, **1991**, *30*, 1320; see also references 2e, 2j, and 2k.

5) M. Nakagawa, T. Kawate, T. Kakikawa, H. Yamada, T. Matsui, and T. Hino, *Tetrahedron*, **1993**, *49*, 1739; for (*S*)-**6**, $[\alpha]_D^{21}$ -14.6° (c 0.50, EtOH).

6) In our previous experiments with an α-phenylethyl derivative,[2c] diastereoselectivity could be explained by the energy difference between diastereomeric β-carbolines, and was controlled thermodynamically.

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