ASYMMETRIC PICTET-SPENGLER REACTION USING α-METHYLBENZYLAMINE AS A CHIRAL AUXILIARY GROUP †

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Abstract - The Pictet-Spengler reaction of chiral *N*-(β-3-indolyl)ethyl-α-methylbenzylamine with aldehydes in the presence of acids in refluxing benzene provided 1-substituted tetrahydro-β-carbolines (~72 % de).

The tetrahydro-β-carbolines and tetrahydroisoquinolines which are structural feature present in many alkaloids are frequently synthesized by the well-known Pictet-Spengler reaction.[1,2] Consequently, the method for carrying out the Pictet-Spengler transformation in asymmetric manner is of important for synthetic organic chemistry. The reported procedures of asymmetric Pictet-Spengler reaction for tetrahydro-β-carboline synthesis involve the use of tryptophan alkyl ester[3~5] or chiral aldehydes [6] as enantiomerically pure starting materials. However, only a few examples which involve the use of subsequently removable chiral auxiliary groups in asymmetric Pictet-Spengler reaction have recently published : Waldmann[7] reported asymmetric Pictet-Spengler reaction of *N*-β-(3-indolyl)ethyl amino acid esters with achiral aldehydes, in which amino acid esters operated as the removable chiral auxiliary groups.

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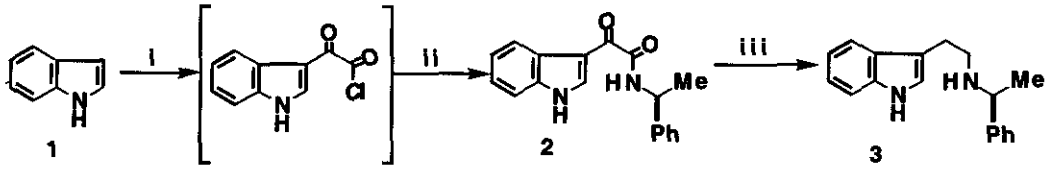
† This paper is dedicated to the memory of the late Professor Yoshio Ban.

In connection with our studies on the synthesis of indole alkaloids, fumitremorgins B[8], C[9] and eudistomines,[10] we have reported the Pictet-Spengler reaction of tryptamine or hydroxytryptamine with aldehyde. The use of chiral amines as a chiral auxiliary[11,12] and chiral building blocks[13] has extensive application in modern synthetic organic chemistry. Thus, the purpose of this paper is to describe the stereoselectivity in asymmetric Pictet-Spengler reaction employing the easily removable methylbenzyl group as a chiral auxiliary.

Scheme 1



i) $(COCl)_2$, ether, room temperature, 2 h
ii) (*S*)-(-)-α-methylbenzylamine, THF, 0°C, 2 h, 77%
iii) $LiAlH_4$, $AlCl_3$, THF, 0°C~room temperature, overnight, 62%

The tryptamine derivative (**3**) which is used as the starting material was easily prepared as follows:[14,15] *N*-acylation of (*S*)-(-)-α-methylbenzylamine with indole-3-oxalyl chloride obtained from indole (**1**) and oxalyl chloride gave N_b-(*S*)-(-)-α-methylbenzyl indole-3-glyoxylamide (**2**) in 77% yield. $LiAlH_4$ reduction of **2** provided the desired tryptamine derivatives (**3**) in 62% yield. Enantiomer of **3** was also synthesized in similar chemical yield, using (*R*)-(+)-α-methylbenzylamine. (Scheme 1)

Since the Pictet-Spengler reaction is generally carried out in the presence of a protic acid,[3] we first tried the Pictet-Spengler cyclization by the reaction of **3** with benzaldehyde (**4a**) in CH_2Cl_2 in the presence of acetic acid (1~15 eq) or trifluoroacetic acid (1~10 eq) at room temperature for 24~48 h and at reflux temperature for 5 h. However the reactions did not proceed, in contrast to *N*-(β-3-indolyl)ethyl substituted amino acid ester.[7] It was also well documented[1] tthat he Pictet-Spengler cyclization could occur in nonacidic and aprotic media to give kinetically controlled products. Therefore, a mixture of **3** and benzaldehyde (**4a**) was refluxed in benzene. β-Carboline (**6a** and **7a**) was obtained in a high yield. However, no diastereoselectivity was observed (Entry 1, Table 1). The Pictet-Spengler products (**6a**) and (**7a**) could not be separated by chromatography, but were separated by fractional crystallizations. The structures were determined by 500 MHz ^{1}H-nmr spectroscopy as well as ^{13}C-nmr and ms spectroscopy. The absolute configuration of these products was confirmed by X-ray analysis of **7a** (Figure and Experimental part). The reaction of **3** with benzaldehyde (**4a**) was further investigated by carrying out in refluxing benzene under a variety of acidic conditions and the results are outlined in Table 1. The

Scheme 2

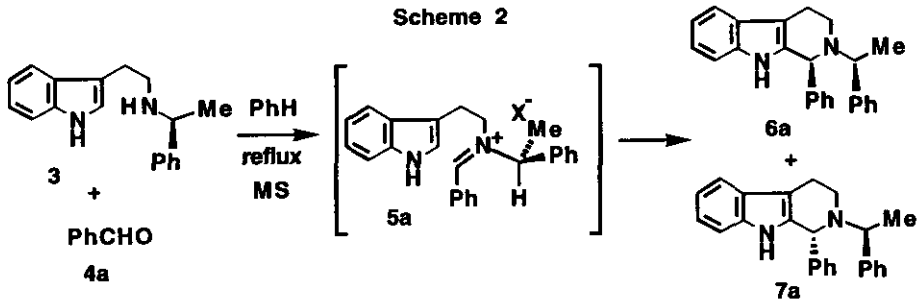
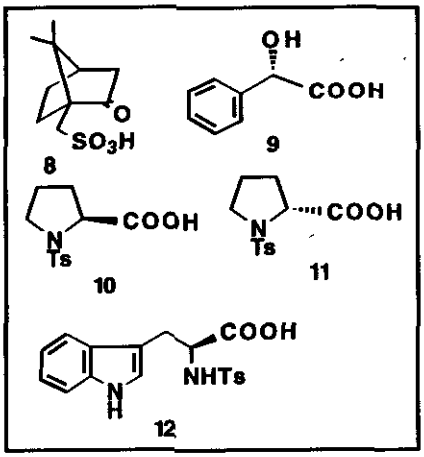


Table 1: *Pictet-Spengler reaction of* 3 *with benzaldehyde* (4a) with various acid in benzene reflux

Entry	Acid (mol eq)	Time (h)	Yield (%) 6a + 7a	Diastereomer Ratio[a] 6a : 7a
1	None	48	96	53 : 47
2	AcOH (1)	24	85	51 : 49
3	TFA (3)	24	39	75 : 25
4	TFA (0.5)	24	71	86 : 14
5	TFA (0.25)	24	96	75 : 25
6	TsOH (1)	48	43	70 : 30
7	HCl in MeOH (0.5)	48	65	52 : 48
8	MsOH (0.05)	48	15	49 : 51
9	8 (0.5)	24	57	47 : 53
10	9 (1)	6	88	52 : 48
11	10 (1)	9	96	46 : 54
12	11 (1)	9	96	42 : 58
13	12(1)	6	96	56 : 44

a) determined by ^{1}H-nmr



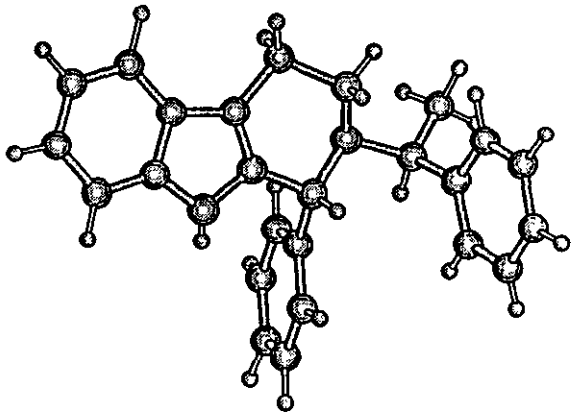


Figure: X-ray structure of 7a

diastereoisomer ratios were determined by ^{1}H-nmr of chromatographically purified mixture of **6a** and **7a** at C-1 protons.

Out of the acids used the best diastereoselectivity was observed by use of trifluoroacetic acid (0.5 eq) (Entry 4, Table 1). It was also found that the amount of trifluoroacetic acid used has a little influence on

the diastereoisomer ratio (Entries 3-5, Table 1). Other acids such as TsOH, MsOH and HCl (in MeOH) did not improve the diastereoisomer ratio (Entries 6-8, Table 1).

In the course of reaction, the iminium intermediate (**5a**) was first formed *in situ* followed by spontaneously cyclized *via* intramolecular attack of the indole nucleus on the iminium functionality to give 1-substituted tetrahydro-β-carboline (**6a**) and (**7a**) (Scheme 2). It was, therefore, anticipated that chiral counter ion X^-, which probably forms ionic bond with positively charged nitrogen, would have an influence for the discrimination of π ($C=N^+$) faces. For this purpose, *d*-camphorsulfonic acid (**8**) was selected as a chiral acid and the Pictet- Spengler reaction was carried out, but the improvement of the diastereoselectivity was not observed (Entry 9, Table 1). In the event, the chiral acids such as (*S*)-mandelic acid (**9**), *N*-tosyl-amino acids (**10**, **11** and **12**) were also used, which surprisingly furnished the Pictet-Spengler products (**6a**) and (**7a**) in high yields within short reaction time. Unfortunately the diastereoselectivity was not increased. However, this is the first examples of the Pictet-Spengler reaction catalyzed by chiral acids such as **8**, **9**, **10**, **11**, and **12** (Entries 9-13, Table 1).

The best diastereoselectivity obtained where TFA (0.5 eq) is used at reflux temperature in benzene (Entry 4, Table 1) was counter-checked, namely, the reaction of an enantiomer of **3** with benzaldehyde (**4a**), giving **ent-6a** and **ent-7a** in the similar chemical yield (71%) and diastereoisomer ratio (84:16), within experimental error.

The Pictet-Spengler reaction of **3** with **4a** was performed in the presence of various Lewis acids. Table 2 is summarizing the screening experiments and shows that different Lewis acids promote the Pictet-Spengler reaction, however, the reaction conditions fail to improve the selectivity.

The effect of solvent on the diastereoselectivity of this reaction was also studied using **3** and benzaldehyde (**4a**) in refluxing solvent with trifluoroacetic acid, and the results were summarized in Table 3. Out of the solvent used, benzene gave the best diastereoisomer ratio with high chemical yield (Entry 1, Table 3).

In order to explore the generality and the scope of the above cyclization, a series of reactions were conducted with various aldehydes under the optimized reaction conditions and the results were outlined in Table 4. The *para*- substituted aromatic aldehyde (i.e., both electron-donating group and electron-withdrawing group) gave no effect to improve the diastereoselectivity as compared to an unsubstituted aldehyde (Entries 1, 2 and 3, Table 4). Alicyclic aldehyde (cyclohexylcarbaldehyde) and aliphatic

Table 2 Pictet-Spengler reaction of 3 with benzaldehyde (4a) with various Lewis acids under the different reaction conditions

Entry	Lewis Acid (mol eq)	Solvent	Temp.	Time (h)	Yield (%) 6a + 7a	Diastereomer Ratio[a] 6a : 7a
1	$B(OPh)_3$ (1)	PhH	reflux	5	96	60 : 40
2	$B(OPh)_3$ (1)	PhH	room temperature	24	77	58 : 42
3	$B(OPh)_3$ (1)	CH_2Cl_2	40°C	48	57	57 : 43
4	$B(OPh)_3$ (1)	CH_2Cl_2	room temperature	96	23	61 : 39
5	$BF_3{\cdot}OEt_2$ (1)	PhH	reflux	24	17	73 : 27
6	$BF_3{\cdot}OEt_2$ (0.5)	PhH	reflux	24	54	71 : 29
7	$BF_3{\cdot}OEt_2$ (1)	CH_2Cl_2	room temperature	48	23	80 : 20
8	$BF_3{\cdot}OEt_2$ (1)	CH_2Cl_2	40°C	48	20	56 : 44
9	$BF_3{\cdot}OEt_2$ (0.5)	CH_2Cl_2	room temperaturet	168	5	56 : 44
10	$Yb(OTf)_3$ (0.05)	CH_2Cl_2	room temperature	168	4	54 : 46
11	$Yb(OTf)_3$ (0.05)	CH_2Cl_2	40°C	48	6	55 : 45
12	$Yb(OTf)_3$ (0.05)	CH_2Cl_2	reflux	24	40	55 : 45
13	$Yb(OTf)_3$ (0.05) $+H_2O$ (2.5)	THF	room temperature then reflux	24 48	NR	------
14	Et_2AlCl (1)	PhH	room temperature	24	51	50:50
15	Et_2AlCl (1)	CH_2Cl_2	room temperature	24	50	67:33
16	Et_2AlCl (1)	CH_2Cl_2	0°C	24	NR	-----
17	Et_2AlCl (1)	CH_2Cl_2	room temperature	0.5	23	67:33

a) determined by ^{1}H-nmr

Table 3 Solvent effect on the Pictet-Spengler reaction of 3 with 4a

Entry	Acid (mol eq)	Solvent	Time (h)	Yield (%) 6a+7a	Diastereomer Ratio[a] 6a : 7a
1	TFA (0.5)	PhH	24	71	86 : 14
2	TFA(1)	MeCN	24	17	78 : 22
3	TFA(1)	Dioxane	24	79	68 : 32
4	TFA(0.5)	PhMe	24	79	66 : 34
5	TFA(0.5)	THF	48	29	55 : 45[b]
6	TFA(0.5)	CH_2Cl_2	48	NR	-----

a) determined by ^{1}H-nmr

b) (R)(+)-1 was used .

Table 4 Results of the reaction of 3 with various aldehyde (4) at refluxing benzene in the presence of CF_3COOH (0.5 mol eq)

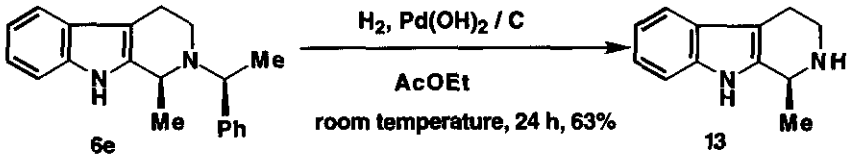
Entry	Aldehyde (2)	Time (h)	Yield (%) 6 + 7	Diastereomer Ratio 6 : 7
1	2a (R=Ph)	24	71	86 : 14[a]
2	2b (R=*p*-$MeOC_6H_4$)	48	39	67 : 33[a]
3	2c (R=*p*-$NO_2C_6H_4$)	24	86	68 : 32[a]
4	2d (R=*c*-C_6H_{11})	48	70	66 : 34[b]
5	2e (R=Me)	24	93	59 : 41[c]
6	2f (R=iBu)	24	58	69 : 31[c]
7	2g (R=*t*-Bu)	24	0	------

a) determined by nmr, b) by hplc, c) by isolation

aldehyde also gave less diastereoselectivity as compared to benzaldehyde itself (Entries 1, 4, 5, and 6, Table 4).

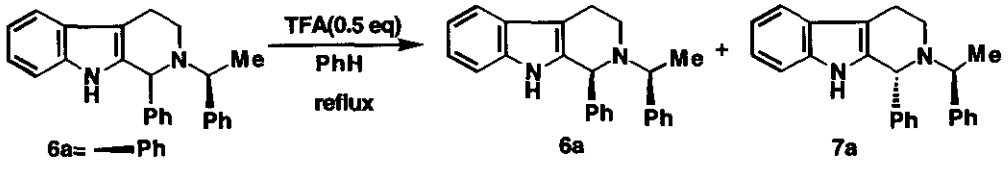
The chiral auxiliary can be removed when **6e** was subjected to hydrogenolysis using $Pd(OH)_2$ on carbon *in AcOEt at room temperature* (Scheme 3). The 1-substituted 1,2,3,4-tetrahydro-β-carboline (**13**) formed was identified with an authentic sample[16] in all respect including optical rotation.

Scheme 3



In the related Pictet-Spengler reaction using tryptophan derivatives in the presence of acid, it was proposed that in these cyclizations the product ratios are results from thermodynamic control.[17,18] On the other hand, kinetically controlled cyclizations are achieved when tryptamine derivatives having chiral auxiliary amino esters were used in the Pictet-Spengler reaction.[7]

Scheme 4



6a= ——Ph

7a= ·····Ph

Table 5 The results of acid catalysed epimerisation on 6a and 7a.

Entry	Substrate	Time (h)	Diastereomer Ratio[a] 6a : 7a
1	7a	6	82 : 18
2	7a	24	82 : 18
3	6a	6	82 : 18

a) determined by ^{1}H-nmr

When the minor stereoisomer (**7a**) was treated with TFA (0.5 eq) in refluxing benzene for 6 h and 24 h, respectively, a mixture of **6a** and **7a** was obtained in the ratio of 82:18 from both reactions, indicating that 6 h reaction time is sufficient for acid catalyzed equilibration. The major isomer (**6a**), likewise, gave the similar ratio (82:18) mixture when treated for 6 h under the similar conditions (Scheme 4 and Table 5). Further mechanistic details and the synthetic utility of these reactions will be reported in due course.

EXPERIMENTAL

Melting points were determined with Yamato MP-1 and Yanagimoto micro melting point apparatus and are uncorrected. Ir spectra (υ in cm^{-1}) were recorded with a Hitachi 260-10 spectrophotometer. Unless otherwise noted, ir spectra refer to KBr disks. Ms were recorded on a Hitachi M-60, RMU-7, JEOL HX-110, or JMS-AM 20 mass spectrometer. Proton and carbon nuclear magnetic resonance (^{1}H- and ^{13}C-nmr) spectra were recorded on JEOL GSX-400, JNM-GSX-500, JNM-GSX-400A, and JNM-GSX-500A apparatus. Nmr spectra were measured in $CDCl_3$, unless otherwise noted, and chemical shifts were recorded in δ values (ppm) relative to Me_4Si internal standard. Optical rotations were recorded with a JASCO DIP-140 polarimeter. Microanalyses were performed on a Perkin Elmer 240 C, H, N analyzer. Silica gel BW-200 or 300 (Fuji-Devison) was used for silica gel column chromatography and Aluminum oxide 90 active basic (Merck) was used for aluminum column chromatography. Hplc analysis was performed on a Hitachi 655 instrument, using a Daicel Chiralcel OD and Hexane : ^{i}PrOH=90 : 10 solvent system was used as a eluent.

(1*S*)-*N*$_b$-α-Phenylethyl Indole-3-glyoxylamide (2)

To a solution of indole **1** (17.57 g, 0.15 mol) in ether (150 ml), $(COCl)_2$ (24.75 ml, 0.195 mol) in ether (100 ml) was added at room temperature and the mixture was stirred for 2 h. Decantation of ether gave yellow solid, which was washed with ether. Yellow solid obtained was dissolved in THF (150 ml) and (*S*)-(-)-α-phenylethylamine (23.5 ml, 0.194 mol) in THF (100 ml) was added to the reaction mixture at 0°C, and the mixture was stirred for 2 h at 0°C. The white crystal **2** (26.28 g, 60%) was collected by filtration. Evaporation and crystallization of mother liquor gave further **2** (7.64 g, 17%). Colorless prisms. mp 205-206°C (*Me*OH). Ir 3300, 3100, 3000, 1680, 1620, 1500, 1440, 1250, 800, 700 cm^{-1}; ^{1}H-nmr (500 MHz) δ: 1.56(1H, br s, N_bH), 1.61(3H, d, *J*=7.1 Hz, Me), 5.15(1H, q, *J*=7.3 Hz, C<u>H</u>MePh), 7.26~7.45(9H, m, aromatic H), 7.80(1H, s, N_a-H); EIms m/z 292(M^+, 8.17), 144(100). Anal. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58. Found: C, 73.88; H, 5.34; N, 9.50.

(S)-*N*-(β-3-Indolyl)-α-phenylethylamine (3)

To a suspension of $LiAlH_4$ (19.97 g, 0.5 mol) in THF (250 ml), $AlCl_3$ (66.66 g, 0.5 mol) was added portionwise at 0°C for 1 h and then (1*S*)-*N*$_b$-α-phenylethyl indole-3-glyoxylamide (**2**)(29.23 g, 0.1 mol) was added portionwise at 0°C for 1 h. After stirring for overnight at room temperature, the reaction mixture was quenched with 20% NaOH while cooling in ice water. The precipitate was filtered and washed with CH_2Cl_2 and the solvent was evaporated after dried over Na_2SO_4. The residue was chromatographed on Al_2O_3 (CH_2Cl_2) and then the product was crystallized from benzene to give white prism **3** (14.16 g, 54%). Evaporation and crystallization of mother liquor gave further **3** (2.21 g, 8%). Colorless prisms. mp 108-109°C (PhH). $[\alpha]_D^{25}$ -61.58° (c 1.0, MeOH). Ir 3400~2800, 1500, 1460, 1240, 1100, 840, 700, 650 cm-^{1}; ^{1}H-nmr (500 MHz) δ: 1.32(3H,

d, *J*=6.4 Hz, Me), 1.58(1H, br s, N_b-H), 2.80~2.94(4H, m, 2xCH_2), 3.78(1H, q, *J*=6.4 Hz, C<u>H</u>MePh), 6.99~7.29(8H, m, aromatic H), 7.35(1H, d, *J*=7.8 Hz, aromatic H), 7.55(1H, d, *J*=7.9 Hz, aromatic H), 7.98(1H, s, N_a-H); LRFABms m/z 265 (M^++H, 100). Anal. Calcd for $C_{18}H_{20}N_2$; C, 81.78; H, 7.63; N, 10.59. Found: C, 81.89; H, 7.57; N, 10.47.

Typical procedure for the Pictet-Spengler reaction: reaction of 3 with benzaldehyde (4a)

To a stirred solution of (1*S*)-*N*-(β-3-indolyl)ethyl-α-phenylethylamine (**3**)(264 mg, 1 mmol) and benzaldehyde (**4a**)(1.1 mmol) in dry benzene (80 ml), trifluoroacetic acid (0.04 ml, 0.5 mmol) was added. The reaction mixture was refluxed for 24 h and *then made alkaline with an excess of 15% aqueous* NaOH. The organic layer was separated, dried over Na_2SO_4, and evaporated. Chromatography of the residue on silica gel(hexane:AcOEt=4:1) afforded a mixture of compound (**6a**) and (**7a**) (250 mg, 71%). Crystallization from methanol gave pure **7a** as colorless prisms. Pure **6a** was obtained from mother liquor by evaporation.

2[(*S*)-α-Phenylethyl]-1-(*S*)-phenyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (6a)

Yellow amorphous. $[\alpha]_D^{24}$ -5.0°(c 1.0, $CHCl_3$). Ir 3400, 3100, 3000, 1500, 1460, 700 cm^{-1}; ^{1}H-nmr (500 MHz) δ: 1.45(3H, d, *J*=6.7 Hz, Me), 2.78(2H, m, 4-CH_2), 3.01(2H, m, 3-CH_2), 3.94(1H, q, *J*=6.7 Hz, C<u>H</u>MePh), 4.92(1H, s, 1-CH), 7.08~7.89(15H, m, aromatic H); ^{13}C-nmr (127 MHz) δ: 14.34(q, Me), 19.99(t, C-4), 41.32(t, C-3), 56.41(d, <u>C</u>HMePh), 60.58(d, C-1), 109.49, 110.74, 118.19, 119.28, 121.42, 127.00, 127.51, 127.78, 127.95, 128.32, 128.35, 128.54, 128.64, 128.75, 128.78, 128.86, 134.50, 136.0, 141.5, 145.0; LRFABms: 353(M^++H, 79), 219(100). HRFABms: Calcd for $C_{25}H_{24}N_2$+H: 353.2619. Found: 353.2003.

2[(*S*)-α-Phenylethyl]-1-(*R*)-phenyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (7a)

Colorless prisms. mp 182-183°C (MeOH). $[\alpha]_D^{24}$ -123.49° (c 1.0, $CHCl_3$). Ir 3400, 3100, 3000, 1500, 1460, 700, 650 cm^{-1}; ^{1}H-nmr (500 MHz) δ: 1.45(3H, d, *J*=6.5 Hz, CH_3), 2.45(1H, m, 4-CH_a), 2.82(2H, m, 4-CH_b and 3-CH_a), 3.36(1H, m, 3-CH_b), 3.92(1H, q, *J*=6.8 Hz, C<u>H</u>MePh), 4.78(1H, s, 1-CH), 7.05~7.49(15H, m, aromatic H); ^{13}C-nmr (127 MHz) δ: 20.45(q, Me), 21.24(t, C-4), 42.29(t, C-3), 57.40(d, <u>C</u>HMePh), 60.97(d, C-1), 108.80, 110.64, 118.18, 119.19, 121.27, 127.01, 127.97, 128.36, 128.76, 135.08, 136.21, 140.62, 142.19; EIms m/z 352(M^+, 16.4), 219 (100). Anal Calcd for $C_{25}H_{24}N_2$: C, 85.19; H, 6.86; N, 7.95. Found: C, 85.19; H, 6.79; N, 7.89. Crystal data for **7a**: $C_{25}H_{24}N_2$, Mw=352.48, monoclinic, space group $P2_1$, a=8.817(1), b=10.450(1), c=10.891(1)Å, α=90.0°, β=102.9°, γ=90.0°. Cell volume: 978.3$Å^3$, Z=2, D_{calcd}=1.197 gcm^{-3}, F(000)=376, Lattice constants and intensity data were measured using graphite-monochromated CuKα(λ=1.5418Å) radiation on Rigaku AFC-5R diffractometer. A total of 1627 unique reflections without $|F_o|$=0 were obtained using ω/2θ scanning method with a 2θ speed of 32° min^{-1} to 0<2θ<120°. The structure was solved by direct method using *SHELX86* and refined to a final R value of 0.0452 and R_w=0.0639.

2[(*S*)-α-Phenylethyl]-1-(*S*)-*p*-methoxyphenyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (6b)

Yellow amorphous. $[\alpha]_D^{24}$ -4.3° (c 1.0, $CHCl_3$). Ir 3400, 3000, 1600, 1500, 700, 650 cm^{-1}; ^{1}H-nmr (500 MHz) δ: 1.43(3H, d, *J*=7.0 Hz, Me), 2.43(1H, m, 4-CH_a), 2.80(2H, m, 4-CH_b and 3-CH_a), 3.50(1H, m, 3-CH_b), 3.84(3H, s, OCH_3), 3.95(1H, q, *J*=7.0 Hz, C<u>H</u>MePh), 4.72(1H, s, 1-CH), 6.82~7.55(14H, m, aromatic H); LRFABms m/z 383(M^++H, 57), 154(100). HRFABms: Calcd for $C_{26}H_{27}N_2O$+H: 383.2125. Found: 383.2118.

2[(*S*)-α-Phenylethyl]-1-(*R*)-*p*-methoxyphenyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (7b)

Colorless prisms. mp 141-142°C (MeOH). $[\alpha]_D^{24}$ -28.5° (c 1.0, $CHCl_3$). Ir 3400, 3000, 1600, 1500, 700, 650 cm^{-1}; ^{1}H-nmr (500 MHz) δ: 1.43(3H, d, *J*=6.7 Hz, Me), 2.77(2H, m, 4-CH_2), 3.00(2H, m, 3-CH_2), 3.77(3H, s, OCH_3), 3.93(1H, q, *J*=6.7 Hz, C<u>H</u>MePh). 4.87(1H, s, 1-CH), 6.82~7.54(14H, m, aromatic H); ^{13}C-nmr (127 MHz) δ: 14.07(q, Me), 20.09(t, C-4), 41.40(t, C-3), 55.27(q, OMe), 56.14(d, <u>C</u>HMePh), 60.03(d, C-1), 109.43, 110.73, 113.90, 118.17, 119.27, 121.37, 126.64, 127.30, 127.51, 128.14, 129.95, 133.89, 134.93, 136.11, 145.31, 159.19; LRFABms m/z 383(M^++H, 70), 154(100). Anal. Calcd for $C_{26}H_{27}N_2O$: C, 81.64; H, 6 .85; N, 7.32. Found: C, 81.58; H, 6.75; N, 7.33.

2[(*S*)-α-Phenylethyl]-1-(*S*)-*p*-nitrophenyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (6c) and 2[(*S*)-α-phenylethyl]-1-(*R*)-*p*-nitrophenyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (7c)

Yellow amorphous. Ir 3400, 2950, 1460, 700, 650 cm^{-1}; ^{1}H-nmr (500 MHz) δ: 1.48(3H, d, *J*=6.7 Hz, CH_3), 2.50~3.50(4H, m, 3-CH_2 and 4-CH_2), 3.84(0.48H, q, *J*=6.7 Hz, C<u>H</u>MePh), 3.89(0.52H, q, *J*=6.5 Hz, C<u>H</u>MePh), 4.94(0.68H, s, 1-CH of **6c**), 4.97(0.32H, s, 1-CH of **7c**), 7.09~8.23(14H, m, aromatic H); LRFABms m/z 359(M^++H, 65), 275(100). HRFABms: Calcd for $C_{25}H_{23}N_2$+H: 359.2489. Found: 359.2464. (The separation of these two diastereoisomer was unsuccessful by either column chromatography or crystallization.)

2[(*S*)-α-Phenylethyl]-1-(*S*)-cyclohexyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (6d) and 2[(*S*)-α-phenylethyl]-1-(*R*)-cyclohexyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (7d)

Yellow amorphous. Ir 3400, 3000, 1600, 1500, 700, 650 cm^{-1}; ^{1}H-nmr (500 MHz) δ: 0.62~1.63 (15H, m, Hs of cyclohexane ring, 1-CH, and CH_3), 2.34~3.53(4H, m, 3-CH_2 and 4-CH_2), 3.63 (1H, q, *J*=6.5 Hz, C<u>H</u>MePh), 7.10~7.71(10H, m, aromatic H). LRFABms m/z 398(M^++H, 32). HREIms: Calcd for $C_{25}H_{23}N_3O_2$: 397.1791. Found: 397.1779. (The diastereoisomer ratio was determined by hplc. The separation of these two diastereoisomer was unsuccessful by either column chromatography or crystallization.)

2[(*S*)-α-Phenylethyl]1-(*S*)-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (6e)

Yellow amorphous. $[\alpha]_D^{25}$ -72.20° (c 1.0, CH_2Cl_2). Ir 3400, 3100, 2900, 1600, 1490, 700, 650 cm^{-1}; ^{1}H-nmr (500 MHz) δ: 1.27(3H, d, *J*=6.8 Hz, CH_3), 1.34(3H, d, *J*=6.7 Hz, CH_3), 2.46 (1H, m, 4-CH_a), 2.78(1H, m, 4-CH_b), 3.07(1H, m, 3-CH_a),

3.22(1H, m, 3-CH_b), 3.80(2H, q, C<u>H</u>MePh and 1-CH), 7.00~7.42(10H, m, aromatic H). LRFABms m/z 291(M^++H, 61), 154(100). HREIms: Calcd for $C_{20}H_{22}N_2$: 290.1784. Found: 290.1788.

2[(*S*)-α-Phenylethyl]-1-(*R*)-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (7e)

Yellow amorphous. $[\alpha]_D^{25}$ -16.90° (c 1.0, CH_2Cl_2). Ir 3400, 3100, 2900, 1600, 1490, 700, 650 cm^{-1}; ^{1}H-nmr (500 MHz) δ: 1.36(6H, d, *J*=6.8 Hz, 2xCH_3), 2.47(1H, m, 4-CH_a), 2.74(2H, m, 4-CH_b and 3-CH_a), 3.05(1H, m, 3-CH_b), 3.86(1H, q, *J*=6.4 Hz, C<u>H</u>MePh), 3.95(1H, q, *J*=6.7 Hz, 1-CH), 7.00~7.51(10H, m, aromatic H); LRFABms m/z 291(M^++H, 48), 105(100). HREIms: Calcd for $C_{20}H_{22}N_2$: 290.1784. Found: 290.1790.

2[(*S*)-α-Phenylethyl]-1-(*S*)-isobutyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-*b*]indole (6f)

Yellow amorphous. $[\alpha]_D^{22}$ -108.5° (c 1.0, $CHCl_3$). Ir 3400, 2950, 1460, 700 cm^{-1}; ^{1}H-nmr (500 MHz) δ: 0.37(3H, d, *J*=6.6 Hz, CH_3), 0.82(3H, d, *J*=6.9 Hz, CH_3), 1.08(1H, m, C<u>H</u>$_a$-iPr), 1.42 (1H, d, *J*=6.6 Hz, CH_3), 1.76(1H, m, C<u>H</u>Me_2), 1.76(1H, m, C<u>H</u>$_b$-iPr), 2.51(1H, m, 4-CH_a), 2.93 (1H, m, 4-CH_b), 3.29(1H, m, 3-CH_a), 3.50(1H, m, 3-CH_b), 3.60(1H, m, 1-CH), 3.78(1H, q, *J*=6.60 Hz, C<u>H</u>MePh), 7.10~7.52(10H, m, aromatic H); LRFABms m/z 333(M^++H, 33), 245 (100). HRFABms: Calcd for $C_{23}H_{28}N_2$: 333.2232. Found: 333.2336.

2[(*S*)-α-Phenylethyl]-1-(*R*)-isobutyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (7f)

Yellow oil. $[\alpha]_D^{22}$ -39.3° (c 1.0, $CHCl_3$). Ir 3400, 2950, 1460, 700 cm^{-1}; ^{1}H-nmr (500 MHz) δ: 0.49(3H, d, *J*=6.6 Hz, CH_3), 0.82(3H, d, *J*=6.6 Hz, CH_3), 1.31(1H, m, C<u>H</u>$_a$-iPr), 1.45(1H, q, *J*=6.3 Hz, CH_3), 1.90(1H, m, C<u>H</u>Me_2), 2.05(1H, m, C<u>H</u>$_b$-iPr), 2.52(1H, m, 4-CH_a), 2.94(1H, m, 4-CH_b), 3.30(1H, m, 3-CH_a), 3.50(1H, m, 3-CH_b), 3.49(1H, m, 1-CH), 3.72(1H, q, *J*=6.45 Hz, C<u>H</u>MePh), 7.10~7.52(10H, m, aromatic H); LRFABms m/z 333(M^++H, 33), 245(100). HRFABms: Calcd for $C_{23}H_{28}N_2$: 333.2232. Found: 333.2343.

1-(*S*)-Methyl-1,2,3,4-tetrahydro-β-carboline (13)

6e (263 mg, 0.896 mmol) was dissolved in AcOEt (15 ml) and subjected to catalytic hydrogenation for 24 h over 20% palladium hydroxide on carbon (0.100 g). The catalyst was removed by filtration, and the filtrate was evaporated under reduced pressure. The residue was chromatographed on silica gel (AcOEt : MeOH = 1:1) to give 1-methyl-1,2,3,4-tetrahydro-β-carboline (**13**) (101 mg, 63 %) as a yellow solid. $[\alpha]_D^{24}$ -51.7° (c 1.0, EtOH). Ir 3400, 2950, 1450, 740 cm^{-1}; ^{1}H-nmr (500 MHz) δ: 1.49(3H, d, *J*=6.6 Hz, CH_3), 2.25(1H, br s, N_b-H), 2.79(2H, m, 4-CH_2), 3.10(1H, m, 3-CH_a), 3.40(1H, m, 3-CH_b), 4.25(1H, q, *J*=6.3 Hz, 1-CH), 7.10(1H, t, *J*=7.8 Hz, aromatic H), 7.16(1H, t, *J*=7.8 Hz aromatic H), 7.32(1H, d, *J*=8.0 Hz, aromatic H), 7.48(1H, d, *J*=7.5 Hz, aromatic H), 7.83(1H, br s, N_a-H).

Acid catalyzed epimerization

To a solution of **7a** (150 mg, 0.426 mmol) in benzene (80 ml), TFA (0.02 ml, 0.25 mmol) was added. The mixture was refluxed for 6 h. Thirty ml portion of the reaction mixture was taken and quenched with 15% NaOH. The organic was separated and dried over Na_2SO_4. After evaporation of solvent, the residue was purified by column chromatography, and the diastereoisomer ratio was determined by ^{1}H-nmr. The same procedure was also carried out on the reaction mixture after 24 h reaction time. Acid catalyzed epimerization of the major stereoisomer (**6a**) was studied by the procedure described above and the results are shown in Table 4.

ACKNOWLEDGMENT

This research was supported by the Ministry of Education, Science, and Culture in the form of a Grant-in-Aid for Scientific Research and the Fujisawa Foundation is gratefully acknowledged. Thanks also due to the Naito Foundation, Fugaku Trust for Medicinal Research, and Japan Research Foundation for Optically Active Compounds. We also thank to Mrs. H. Seki, Miss R. Hara, Mrs S. Yamada, and Mr. T. Kuramochi in the Analytical Center of Chiba University for measurements of spectral data (nmr and ms) and elemental analyses.

REFERENCES AND NOTES

1. (a) F. Ungemach and J. M. Cook. *Heterocycles*, **1978**, 9, 1089; b) X. Fu and J. M. Cook, *J. Am. Chem. Soc.*, **1992**, 114, 6910.
2. "Isoquinolines" in "The Chemistry of Heterocyclic Compounds" Vol. 38, Part I, Ed., G. Grethe, **1981**, Wiley, New York.
3. (a) P. D. Bailey, S. P. Hollinshead, N. R. Mclay, K. Morgan, S. J. Palmer, S. N. Prince, C. D. Reynolds, and S. D. Wood, *J. Chem. Soc., Perkin Trans.* I, **1993**, 431 and references therein; (b) L. Deng, K. Czerwinski, and J. M. Cook, *Tetrahedron Lett.*, **1991**, 32, 175 and references therein; (c) G. Massiot and T. Mulumba, *J. Chem. Soc., Chem. Commun.*, **1983**, 1147; (d) S. Peng and E. Winterfeldt, *Liebigs Ann. Chem.*, **1990**, 313; (e) L. H. Zhang, Y. Z. Bi, F. X. Yu, G. Menzia, and J. M. Cook, *Heterocycles*, **1992**, 34, 517.
4. P. D. Bailey, M. H. Moore, K. M. Morgan, D. I. Smith, and J. M. Vernon, *Tetrahedron Lett.*, **1994**, 35, 3587.
5. P. H. H. Hermken, J. H. van Maarseveen., P. L. H. M. Cobben, H. C. J. Ottenheijm, C. G. Kruse, and H. W. Scheeren, *Tetrahedron*, **1990**, 46, 833.

6. (a) Z. Czarnocki., D. B. MacLean, and W. A. Szarek, *Bull. Soc. Chim. Belg.*, **1986**, 95, 749 and references therein; (b) P. Melnyk, P. Ducrot, and C. Thal, *Tetrahedron*, **1993**, 49, 8589.

7. (a) H. Waldmann, G. Schmidt, M. Jansen, and J. Geb, *Tetrahedron Lett.*, **1993**, 34, 5867 and the references cited therein; (b) H. Waldmann, G. Schmidt, M. Jansen, and J. Geb, *Tetrahedron*, **1994**, 50, 11865.

8. (a) M. Nakagawa, S. Kodato, M. Hongu, T. Kawate, and T. Hino, *Tetrahedron Lett.*, **1986**, 27, 6217; (b) M. Nakagawa, H. Fushima, T. Kawate, M. Hongu, T. Une, S. Kodato, M. Taniguchi, and T. Hino, *Chem. Pharm. Bull.*, **1989**, 37, 23.

9. T. Hino, T. Kawate, and M. Nakagawa, *Tetrahedron.*, **1989**, 45, 1941.

10. (a) M. Nakagawa, J. Liu, K. Ogata, and T. Hino, *J. Chem. Soc., Chem. Commun.*, **1988**, 463; (b) M. Nakagawa, J. Liu, T. Hino, *J. Am. Chem. Soc.*, **1989**, 111, 2721; (c) J. Liu, M. Nakagawa, and T. Hino, *Tetrahedron*, **1989**, 45, 7729; (d) T. Hino, A. Hasegawa, J. Liu, and M. Nakagawa,. *Chem. Pharm. Bull.*, **1990**, 38, 59; (e) J. Liu, M. Nakagawa, N. Harada, A. Tsuruoka, A. Hasegawa, J. Ma, and T. Hino, *Heterrocycles*, **1990**, 31, 229; (f) J. Liu, M. Nakagawa, K. Ogata, and T. Hino, *Chem. Pharm. Bull.*, **1991**, 39, 1672.

11. (a) K. Hareda, Asymmetric Synthesis, Ed., J. D. Morrison, Vol 5, pp. 359-383, **1985**, Academic Press, New York; (b) M. Pfau, G. Revial, A. Guingant, and J. Angelo. *J. Am. Chem. Soc.*, **1985**, 107, 273; (c) A. W. Frahm and G. Knupp, *Tetrahedron Lett.*, **1981**, 22, 2633; (d) D. E. Nichols, C. F. Burfknecht, and D. B. Rusterholz, *J. Med. Chem.*, **1973**, 16, 480; (e) M. S. Reddy and J. M. Cook, *Tetrahedron Lett.*, **1994**, 35, 5413.

12. (a) P. D. Bailey, G. F. Brown, F. Korber, A. Reed, and R. D. Wilson, *Tetrahedron: Asymmetry*, **1991**, 2, 1263; (b). D. Larsen and P. A. Grieco, *J. Am. Chem. Soc.*, **1985**, 107, 1768.

13. M. Tamura, S. Shiono, and K. Harada, *Bull. Chem. Soc. Jpn.*, **1989**, 62, 3828.

14. R. Stauffer, *Helv. Chim. Acta*, **1966**, 49, 1199.

15. T. Kametani, S. Takano, S. Hibino, and M. Takeshita, *Synthesis*, **1972**, 475.

16. H. Akimoto, K. Okamura, M. Yui, T. Shioiri, H. Kuramoto, Y. Kikugawa, and S. Yamada, *Chem. Pharm. Bull.*, **1974**, 22, 2614.

17. P. D. Bailey, *Tetrahedron Lett.*, **1987**, 28, 5181.

18. L. Deng, K. Czerwinski, and J. M. Cook, *Tetrahedron Lett.*, **1991**, 32, 175.

Received, 29th March, 1995