HETEROCYCLES, Vol. 59, No. 2, 2003, pp. 691 - 705, Received, 29th October, 2002

A FACILE SYNTHSIS OF 1,1-DISUBSTITUTED 1,2,3,4-TETRAHYDRO-β-CARBOLINES *VIA* TRIFLUOROACETIC ACID CATALYZED PICTET-SPENGLER REACTION USING TITANIUM(IV) ISOPROPOXIDE AS AN IMINATION REAGENT

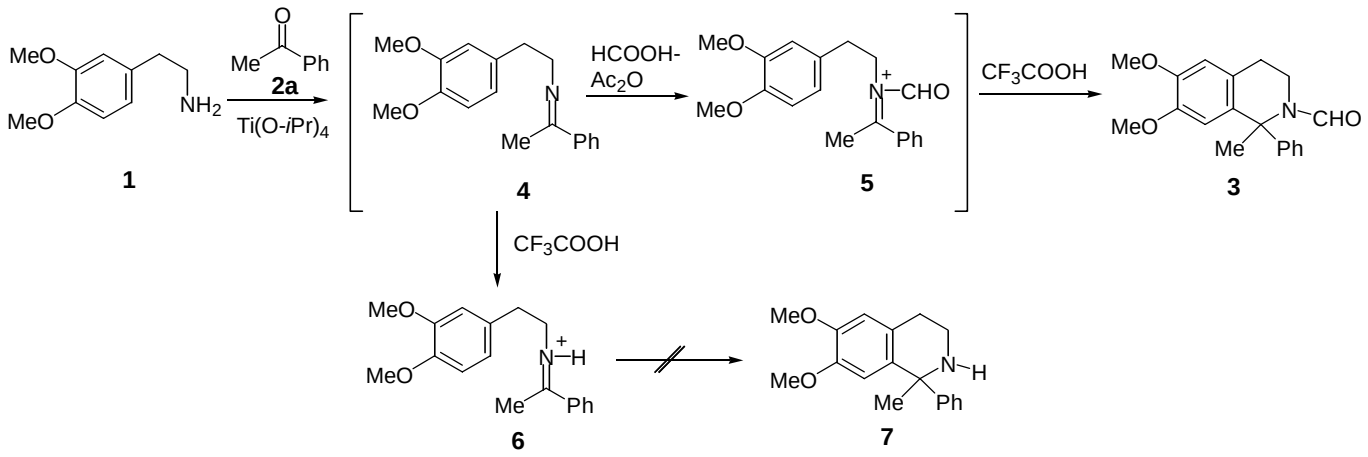
Yoshie Horiguchi,* Masayoshi Nakamura, Akiko Kida, Hirokazu Kodama, Toshiaki Saitoh, and Takehiro Sano

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

Abstract - A synthesis of 1,1-disubstitued 1,2,3,4-tetrahydro-β-carbolines (**13**) was achieved in a highly effective manner *via* the trifluoroacetic acid catalyzed Pictet-Spengler reaction of the keto imines (**9**) prepared from tryptamine (**8**) with acyclic and cyclic ketones using titanium(IV) isopropoxide as the imination reagent under one pot procedure. This reaction provides a convenient and general method for preparing various 1,2,3,4-tetrahydro-β-carbolines derivatives.

Recently, we have developed a convenient method of preparing 1,1-disubstituted 1,2,3,4-tetrahydroisoquinolines *via* Pictet-Spengler reaction[1] of arylethylamines with ketones using titanium(IV) isopropoxide which overcame the difficulty of imination reaction.[2] The cyclization of the imines to the isoquinoline ring system catalyzing with trifluoroacetic acid (TFA) proceeded in a highly

effective manner *via* the formyliminium ion *in situ* formed with acetic-formic anhydride. For example, the reaction of 2-(3,4-dimethoxyphenyl)ethylamine (**1**) with acetophenone (**2a)** produced the corresponding *N*-formyl-1,2,3,4-tetrahydroisoquinoline (**3**) in 99% yield. We also found that the Pictet-Spengler reaction of arylethylamines with ketones does not proceed *via* the iminium ion (**6**) generated from the imine (**4**) by protonation (Scheme 1). In this paper we describe the Pictet-Spengler reaction of tryptamine with ketones using titanium (IV) isopropoxide, which would provide a method of preparing 1,1-substituted 1,2,3,4-tetrahydro-β-carbolines.[3]

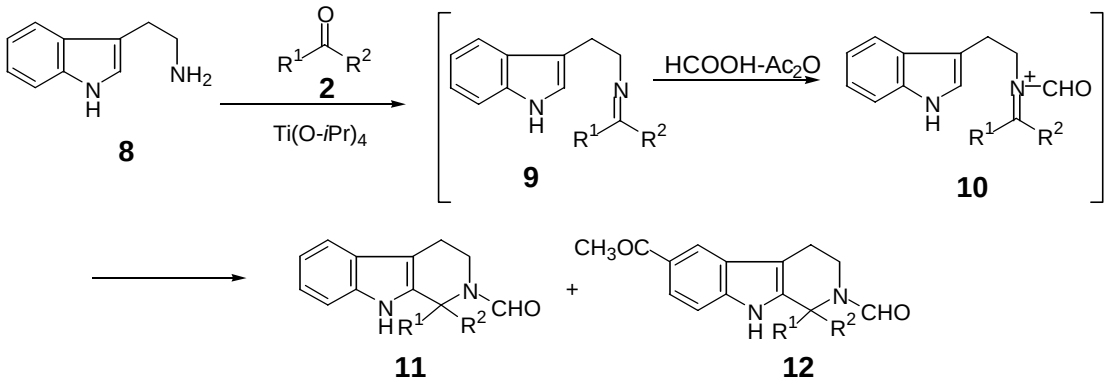


Scheme 1

Results and Discussions

The mixture of tryptamine (**8**) (1.2 mol eq.), acetophenone (**2a**) (1 mol eq.) and titanium(IV) isopropoxide (1.5 mol eq.) was heated at 80°C for 3 h and then to this mixture a large excess amount of acetic-formic anhydride (prepared from formic acid 100 mol eq.: acetic anhydride 100 mol eq.) was added, and the solution was heated at 70°C for 3 h. This mixture was further treated with TFA (200 mol eq) under heating at 70°C for 3 h. Thus, the reaction yielded two products, *N*-formyl-1-methyl-1-phenyl-1,2,3,4-tetrhydro-β-carboline (**11a**) in 73% and the other is 6-acetyl derivative (**12a**) in 27% yield (Table 1, Run 1). This result demonstrated that the reaction, although it induced the cyclization leading to the carboline ring system in a quantitative manner, causes the acetylation of the initially formed β-carboline (**11a**) at C6. The similar reaction of **8** with acetone (**2b**) produced

N-formyl-1,1-dimethyl-1,2,3,4-tetrahydro-β-carboline (**11b**) in 39% yield (Table 1, Run 2). Prolonged reaction gave 6-acetyl derivative (**12b**)[4] as a sole product in 83 % yield instead of **11b** (Table 1, Run 3).



Scheme 2

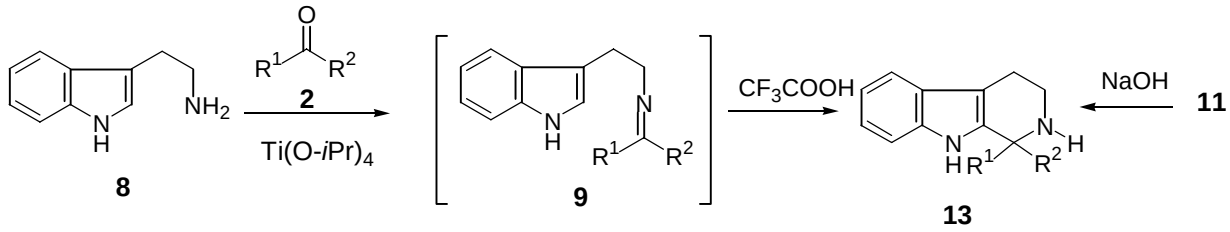
Table 1. Synthesis of *N*-Formyl-1,1-disubstituted Tetrahydro-β-carbolines (**11**)

Run	Ketones	R^1	R^2	Reagent (mol eq.) Ac_2O	HCOOH	CF_3COOH	Conditions Temp.	Time (h)	Products yields (%) **11**	(%)	**12**	(%)
1	**2a**	Me	Ph	100	100	200	70	3	**11a**	73	**12a**	27
2	**2b**	Me	Me	100	100	200	70	3	**11b**	39	--	
3	**2b**	Me	Me	100	100	200	70	18	--		**12b**	83
4	**2a**	Me	Ph	100	300		70	18	**11a**	53		
5	**2b**	Me	Me	100	300		70	18	**11b**	49		
6	**2c**	Me	Et	100	300		70	18	**11c**	61		
7	**2d**	Me	CH_2SPh	100	300		70	18	**11d**	51		
8	**2e**	Ph	Ph	100	300		70	18	**11e**	27		
9	**2f**			100	300		70	18	**11f**	52		
10	**2g**			100	300		70	18	**11g**	9		
11	**2h**			100	300		70	18	**11h**	24		

Next, we investigated the reaction under the relatively weak acidic condition using formic acid instead of TFA, which may avoid the undesired acetylation reaction at the indole ring, and found that the formyliminium ion (**10**), when treated with formic acid, caused the expected cyclization without accompanying the undesired reaction. Thus, the treatment of formyliminium ion (**10a**) *in situ* prepared from **8** and acetophenone (**2a**) with formic acid (200 mol eq.) under heating at 70 °C for 18 h afforded **11a** as a sole product, although the yield was relatively low (53%) (Table 1, Run 4). Several attempts of

improving the yield were unsuccessful. As judged from reaction time the cyclization of **10** in formic acid is relatively slow and seems to reach a plateau at 18 h. At longer reaction time (40 h) the yield of **11a** was decreased (45%). The reactions of **8** with acyclic ketones (**2b**-**e**) and cyclic ketones (**2f**-**h**) also gave the corresponding *N*–formyl-β-carbolines (**11b**-**h**) as a sole product, in moderate to low yields (Table 1, Rruns 5-11).

Finally, we found that the Pictet-Spengler cyclization of **8** with ketones occurs from the imine (**9**) to yield β-carboline (**13**) directly. The solution of imine (**9a**) *in situ* prepared by condensation of **8** with acetophenone (**2a**) in the presence of titanium(IV) isopropoxide was treated with excess amount of TFA (100 mol eq.) under heating at 80 °C for 3 h to give **13a** in 99% yield (Table 2, Run 1). The use of formic acid instead of TFA and a longer reaction time (18 h) gave **13a** in 70% yield (Table 2, Run 2). The fact



Scheme 3

Table 2. Synthesis of 1,1-Disubstituted Tetrahydro-β-carbolines (**13**)

Run	Ketones	R^1	R^2	Acid	Temp. (°C)	Time (h)	Products	Yield (%)
1	**2a**	Me	Ph	CF_3COOH	70	3	**13a**	99
2	**2a**	Me	Ph	HCOOH	70	18	**13a**	70
3	**2b**	Me	Me	CF_3COOH	70	3	**13b**	91
4	**2c**	Me	Et	CF_3COOH	70	3	**13c**	93
5	**2d**	Me	CH_2SPh	CF_3COOH	70	3	**13d**	69
6	**2e**	Ph	Ph	CF_3COOH	70	3	**13e**	57
7	**2f**			CF_3COOH	70	3	**13f**	72
8	**2g**			CF_3COOH	70	3	**13g**	76
9	**2h**			CF_3COOH	70	3	**13h**	12

indicated that the increasing acidity of the reaction medium accelerated the Pictet-Spengler cyclization as shown in the dication chemistry reported by Shudo *et al.*[5]

The reaction of **8** with acetone (**2b**), ethyl methyl ketone (**2c**), 1-phenylsulfanylproan-2-one (**2d**), benzophenone (**2e**), cyclopentanone (**2f**), and cyclohexanone (**2g**) gave the corresponding 1,1-disubstituted tetrahydro-β-carbolines (**13b-g**) in excellent to good yields, although indanone gave the β-carboline (**13h**) only in 14% yield (Table 2, Run 9). It is worthy to note that this reaction of **8** by using titanium(IV) isopropoxide and TFA caused the Pictet-Spengler cyclization even in the cases of highly sterically congested ketones such as diphenyl ketone and indanone.

Alkaline hydrolysis of the *N*-formate (**11**) with NaOH yielded **13** in good yields (see EXPERIMENTAL) except that of the 1,1-diphenyl derivative (**11e**) which was resistant to this hydrolysis because of the steric hindrance of the phenyl groups at C1.

Thus, the Pictet-Spengler reaction of tryptamine with ketones using titanium(IV) isopropoxide and TFA provides a convenient and highly effective method of synthesizing various 1,1-disubstituted 1,2,3,4-tetrahydro-β-carbolines.

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 KBr disks for solids with a HORIBA FT-710 spectrophotometer, and the values are given in cm^{-1}. NMR spectra were measured on a JEOL JNM-AL 300 (^{1}H-NMR, 300 MHz; ^{13}C-NMR, 75 MHz) NMR spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard and the chemical shifts are given in δ values. LR-MS were taken on JMS-AM20, and high resolution MS (HR-MS) on a JEOL JMS-D300 spectrometer at 70 eV (EI-MS) or at 270 eV [(CI-MS), reactant gas: *iso*-butane] using direct or GC/MS inlet systems. FAB-MS spectra were recorded with JEOL-HX100A spectrometer using glycerol as a matrix. Elemental analyses were recorded on a Yanaco-CHN-corder MT-3. TLC was

performed on Merck precoated Silica gel 60 F_{254} plates (Merck). Column chromatography was carried out with silica gel (Wakogel C-200) or aluminum oxide (aluminum oxide 90, Merck). The organic extract from each reaction mixture was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to dryness.

The Pictet-Spengler Reaction of Tryptamine (8) with Ketones (2) under Formylation Reaction Condition Using Trifluoroacetic Acid.

Reaction with 2a (Table 1, Run 1): A mixture of **8** (1.00 g, 6 mmol), acetophenone (**2a**) (0.62 g, 5.2 mmol) and Ti(O-*i*Pr)$_4$ (2.22 g, 7.8 mmol) was heated at 80°C for 3 h under an argon atmosphere. To the reaction mixture, a solution of acetic-formic anhydride [prepared from HCOOH (24 g, 0.52 mol) and Ac_2O (53 g, 0.52 mol)] was added at 0°C, then the mixture was heated at 70°C for 2 h. To this reaction mixture CF_3COOH (119 g, 1.04 mol) was added and heated at 70°C for 3 h. The reaction mixture was diluted with MeOH (100 mL) and passed through a short SiO_2 column ($CHCl_3$-MeOH) to remove TiO_2. The eluent was concentrated *in vacuo* to *ca*. 50 mL and the residue was extracted with $CHCl_3$. After removal of the solvent of extract *in vacuo*, the residue was purified by chromatography over SiO_2 (AcOEt-hexane (1:1)) to give **11a** (1.10 g, 73%) and **12a** (0.466 g, 27%).

2-Formyl-1-methyl-1-phenyl-1,2,3,4-tetrahydro-β-carboline (11a)

Colorless plates recrystallized from MeOH-hexane, mp: 206-209℃. IR: 1637, 1493. ^{1}H-NMR: 2.10, 2.23 (3H, each s, CH_3), 2.92-3.01 (2H, m, 4-H), 3.65-3.71, 4.21-4.28 (total 2H, each m, 3-H), 7.1-7.4 (8H, m, PhH), 7.55 (1H, d, *J*= 8 Hz, 5-H), 8.12, 8.16 (total 1H, s, CHO). ^{13}C-NMR: 20.8 (C4), 26.3 (CH_3), 36.2 (C3), 61.0 (C1), 109.1 (C4a), 111.1 (C8), 118.4 (C7), 119.7 (C5), 122.2 (C6), 126.4 (C4b), 127.1 (Ph-CHx2), 128.1 (Ph-CH), 128.8 (Ph-CHx2), 136.4 (C8a and C9a), 142.7 (Ph-C), 162.1 (CHO). LR-EIMS (*m/z*): 290 (M^+), 57 (base peak). HR-EIMS *m/z* (M^+): Calcd for $C_{19}H_{18}N_2O$: 290.1416. Found: 290.1408. *Anal*. Calcd for $C_{19}H_{18}N_2O$: C, 78.36; H, 6.33; N, 9.52. Found: C, 78.59; H, 6.25; N, 9.65.

6-Acetyl-2-formyl-1-methyl-1-phenyl-1,2,3,4-tetrahydro-β-carboline (12a)

Colorless prisms crystallized from AcOEt-hexane, mp: 250-253°C. IR: 1647. ^{1}H-NMR: 2.13 (3H, s, CH_3), 2.66 (3H, s, $COCH_3$), 3.0-3.1 (2H, m, 4-H), 3.65-3.73, 4.3-4.4 (total 2H, m, 3-H), 7.24 (1H, d, *J*=8.5 Hz, 8-H), 7.3-7.4 (5H, m, Ph), 7.83 (1H, dd, *J*=8.5 Hz, 1.5 Hz, 7-H), 8.16 (1H, s, CHO), 8.21 (1H, d, *J*=1.5 Hz, 5-H), 8.29 (1H, br s, Ar-N<u>H</u>). ^{13}C-NMR: 20.8 (C4), 26.2 (CH_3), 26.6 (CO<u>C</u>H_3), 36.0 (C3), 61.0 (C1), 110.4 (C4a), 111.0 (C8), 120.6 (C7), 122.6 (C5), 126.0 (C4b), 127.0 (Ph-CHx2), 128.3(Ph-CH), 128.9 (Ph-CHx2), 130.0 (C6), 138.3 (C9a), 139.2 (C8a), 142.2 (Ph-C), 162.2 (CHO), 198.4 (<u>C</u>OCH_3). EI-LRMS (*m/z*): 332 (M^+), 58 (base peak). HR-EIMS *m/z* (M^+): Calcd for $C_{21}H_{20}N_2O_2$: 332.1525. Found: 332.1558.

Reaction with 2b (Table 1, Run 2). The reaction of **8** (1.00 g, 6 mmol) with **2b** (0.38 g, 5.2 mol) gave **11b** (0.48g, 39%) under similar reaction condition.

2-Formyl-1,1-dimethyl-1,2,3,4-tetrahydro-β-carboline (11b)

Colorless plates recrystallized from AcOEt-hexane, mp: 188-190°C. IR: 1635. ^{1}H-NMR: 1.79, 1.88, 2.00 (total 6H, each s, CH_3x2), 2.7-2.9 (2H, m, 4-H), 3.62, 4.00 (total 2H, each t, *J*=6 Hz, 3-H), 7.1-7.2 (2H, m, 6-H and 7-H), 7.34 (1H, d, *J*=8 Hz, 5-H), 7.49 (1H, d, *J*=8 Hz, 8-H), 8.05 (1H, br s, Ar-N<u>H</u>), 8.63, 8.69 (total 1H, each s, -C<u>H</u>O). ^{13}C-NMR: 21.0 (C4), 29.0(CH_3x2), 35.9 (C3), 55.6 (C1), 108.6 (C4a), 110.9 (C8), 118.4 (C7), 119.8 (C5), 122.3 (C6), 126.6 (C4b), 136.0 (C9a), 136.9 (C8a), 160.6 (CHO). LR-EIMS (*m/z*): 228 (M^+), 213 (base peak). HR-EIMS *m/z* (M^+): Calcd for $C_{14}H_{16}N_2O$: 228.1263. Found: 228.1278. *Anal*. Calcd for $C_{14}H_{16}N_2O$: C, 73.46; H, 7.12; N, 12.08. Found: C, 73.66; H, 7.06; N, 12.27.

Reaction with 2b (Table 1, Run 3). The reaction of **8** (1.00 g, 6 mmol) with **2b** (0.38 g, 5.2 mol) gave **12b** (1.16g, 83%) under heating for 18 h.

6-Acetyl-2-formyl-1,1-dimethyl-1,2,3,4-tetrahydro-β-carboline (12b)

A Pale yellow gum. IR: 2360, 1647. ^{1}H-NMR: 1.75, 1.83 (total 6H, each s, CH_3x2), 2.67, 2.70 (total 3H, each s, $COCH_3$), 2.83 (2H, t, *J*=6 Hz, 4-H), 3.65, 4.01 (total 2H, each t, *J*=6 Hz, 3-H), 7.35, 7.52 (total 1H, each d, *J*=8 Hz, 8-H), 7.7-7.9 (1H, m, 7-H), 8.09, 8.17 (total 1H, each d, *J*=1 Hz, 5-H), 8.31, 8.64 (total

1H, each s, CHO), 8.86, 9.14 (total 1H, each br s, Ar-NH). LR-EIMS: *m/z* 270 (M^+), 255 (base peak). HR-EIMS *m/z* (M^+): Calcd for $C_{16}H_{18}N_2O_2$: 270.1380. Found: 270.1369.

Hydrolysis of 12b[4]

A solution of **12b** (140 mg, 0.52 mmol) in 10% HCl-MeOH (5 mL) was stirred for 12 h at rt. The solution was basified with 10% NaOH solution and the mixture was extracted with $CHCl_3$. The residue was purified by chromatography over Al_2O_3 (AcOEt-hexane (1:1)) to give 6-acetyl-1,1-dimethyl-1,2,3,4-tetrahydro-β-carboline (35 mg, 28%) as pale yellow prisms recrystallized from AcOEt-hexane, mp 193-196°C. IR: 3214, 2962, 1652. ^{1}H-NMR: 1.50, 1.52 (total 6H, each s, CH_3x2), 2.63, 2.68 (total 3H, each s, $COCH_3$), 2.7-2.8 (2H, m, 4-H), 3.21-3.24 (2H, m, 3-H), 7.32, 7.49 (total 1H, each d, *J*=8 Hz, 9 Hz, 8-H), 7.73, (dd, *J*=1 Hz, 8 Hz), 7.82 (dd, *J*=2 Hz, 9 Hz): total 1H, 7-H, 8.02, (d, J=1 Hz), 8.15 (d, *J*=2 Hz): total 1H, 5-H, 8.14, 8.28 (total 1H, each br s, Ar-NH). ^{13}C-NMR: 22.8 (C4), 26.7, 26.7 ($CO\underline{C}H_3$), 28.8 (CH_3x2), 50.5, 50.7(C1), 108.0, 109.0 (C4a), 110.5, 117.7 (C8), 111.8, 120.3 (C7), 120.0, 122.1 (C5), 127.1, 129.2 (C6), 130.7, 131.3 (C4b), 135.0, 138.5 (C9a), 142.2, 145.2 (C8a), 198.8(s, $\underline{C}OCH_3$). LR-EIMS (*m/z*): 242 (M^+), 227 (base peak). HR-EIMS *m/z* (M^+): Calcd for $C_{15}H_{18}N_2O$: 242.1431. Found: 242.1420.

Synthesis of 2-Formyl-1,1-disubstitued 1,2,3,4-Tetrahydro-β-carbolines (11). Typical Procedure: A mixture of **8** (1.00 g, 6 mmol), **2a** (0.62 g, 5.2 mmol) and Ti(O-*i*Pr)$_4$ (2.22 g, 7.8 mmol) was heated at 80°C for 3 h under an argon atmosphere. To the reaction mixture, a solution of acetic-formic anhydride [prepared from HCOOH (71.76 g, 1.56 mol) and Ac_2O (53 g, 0.52 mol)] was added at 0°C, then the mixture was heated at 70°C for 18 h. The reaction mixture was diluted with MeOH (100 mL) and passed through a short SiO_2 column ($CHCl_3$-MeOH) to remove TiO_2. The eluent was concentrated *in vacuo* to *ca*. 50 mL and the residue was extracted with $CHCl_3$. After removal of the solvent of extract *in vacuo*, the residue was purified by chromatography over SiO_2 (AcOEt-hexane (1:1)) to give **11a** (0.80 g, 53%).

1-Ethyl-2-formyl-1-methyl-1,2,3,4-tetrahydro-β-carboline (11c) (768 mg, 61%) was obtained from **8**

(1.00 g, 6 mmol) and **2c** (0.38, 5.2 mmol) as colorless needles recrystallized from MeOH-hexane, mp:162-164℃. IR: 1631, 1491. ^{1}H-NMR: 0.64, 0.79 (total 3H, each t, *J*=7 Hz, $CH_2C\underline{H}_3$), 1.74, 1.80 (total 3H, each s, CH_3), 2.06-2.18, 3.13-3.18 (total 2H, each m, -$C\underline{H}_2CH_3$), 2.80-2.87, 3.52-3.60 (total 2H, each m, H-4), 3.69-3.76, 3.89-4.02 (total 2H, each m, 3-H), 7.10-7.26 (2H, m, 6-H and 7-H), 7.35 (1H, d, *J*=8 Hz, 8-H), 7.50 (1H, d, *J*=8 Hz, 5-H), 8.15, 8.22 (total 1H, each br s, Ar-N$\underline{H}$), 8.33, 8.53 (total 1H, each s, CHO). ^{13}C-NMR: 8.0 ($CH_2\underline{C}H_3$), 20.7 (C4), 27.6 (CH_3), 33.4 ($\underline{C}H_2CH_3$), 36.3 (C3), 59.0 (C1), 109.4 (C4a), 110.9 (C8), 118.2 (C7), 119.5 (C5), 122.0 (C6), 126.4 (C4b), 135.9 (C9a), 136.2 (C8a), 161.3 (CHO). EI-LRMS (*m/z*): 242 (M^+), 213 (base peak). HR-EIMS *m/z* (M^+): Calcd for $C_{15}H_{18}N_2O$: 242.1419. Found: 242.1445. *Anal*. Calcd for $C_{15}H_{18}N_2O$: C, 74.17; H, 7.62; N, 11.74. Found: C, 74.35; H, 7.49; N, 11.56.

2-Formyl-1-methyl-1-phenylsulfanyl-1,2,3,4-tetrahydro-β-carboline (11d) (891 mg , 51%) was obtained from **8** (1.00 g, 6 mmol) and **2d** (0.86 g, 5.2 mmol) as pale yellow plates recrystallized from MeOH-hexane, mp: 179-181℃. IR: 1639, 1510. ^{1}H-NMR: 1.87, 1.90 (total 3H, each s, CH_3), 2.74-2.90 (2H, m, 4-H), 2.94-3.06, 3.78-3.86, 4.41-4.57 (total 2H, each m, 3-H), 3.47, 3.56 (total 1H, each d, *J*=14 Hz, CH_2S), 3.67, 4.38 (total 1H, each d, *J*=13 Hz, CH_2S), 7.0-7.4 (8H, m, PhH), 7.49 (1H, d, *J*=8 Hz, 5-H), 8.07, 8.19 (total 1H, br s, Ar-N$\underline{H}$), 8.23, 8.62 (total 1H, each s, CHO). ^{13}C-NMR: 20.9 (C4), 24.8 (CH_3), 35.8 (C3), 45.4 (CH_2S), 58.9 (C1), 109.1 (C4a), 111.7 (C8), 118.4 (C7), 119.6 (C5), 122.3 (C6), 126.2 (C4b), 127.0 (Ph-CH), 129.0 (Ph-CHx2), 130.7 (Ph-CHx2), 135.2 (C9a), 135.5 (Ph-C), 136.2 (C8a), 161.1 (CHO). RL-EIMS (*m/z*): 336 (M^+), 213 (base peak). HR-EIMS *m/z* (M^+): Calcd for $C_{20}H_{20}N_2OS$: 336.1293. Found: 336.1275. *Anal*. Calcd for $C_{20}H_{20}N_2OS$: C, 71.16; H, 6.01; N, 8.19. Found: C, 71.40; H, 5.99; N, 8.33.

2-Formyl-1,1-diphenyl-1,2,3,4-tetrahydro-β-carboline (11e) (494 mg, 27%) was obtained from **8** (1.00 g, 6 mmol) and **2e** (0.96 g, 5.2 mmol) as colorless plates recrystallized from MeOH-hexane, mp: 266-268℃. IR:1658, 1583. ^{1}H-NMR: 2.97-3.06 (total 2H, each t, *J*=6 Hz, 4-H), 3.62, 3.84 (total 2H, each

t, *J*=6 Hz, H-3), 7.1-7.4 (13H, m, PhH), 7.57 (1H, d, *J*=7 Hz, 5-H), 7.88 (1H, br s, Ar-NH), 8.17 (1H, s, CHO). ^{13}C-NMR: 20.9 (C4), 36.4 (C3), 69.1 (C1), 110.6 (C4a), 111.2 (C8), 118.7 (C7), 119.7 (C5), 122.5 (C6), 126.3 (C4b), 128.4 (Ph-CHx2), 28.7 (Ph-CHx4), 128.9 (Ph-CHx4), 135.1 (C9a), 136.4 (C8a), 140.5 (Ph-C), 162.4 (CHO). LR-EIMS (*m/z*): 352 (M^+), 58 (base peak). HR-EIMS *m/z* (M^+): Calcd for $C_{24}H_{20}N_2O$: 352.1576. Found: 352.1606. *Anal*. Calcd for $C_{24}H_{20}N_2O$: C, 81.68; H, 5.89; N, 7.65. Found: C, 81.79; H, 5.72; N, 7.95.

2-Formyl-1,2,3,4-tetrahydro-β-carboline-1-spirocyclopentane (11f) (611 mg, 52 %) was obtained from **8** (1.00 g, 6 mmol) and **2f** (0.44g, 5.2 mmol) as colorless plates recrystallized from MeOH-hexane, mp: 246-248℃ IR: 1631, 1585. ^{1}H-NMR: 1.89-2.36 (8H, m, 2'-H, 3'-H, 4'-H and 5'-H), 2.82, 2.86 (total 2H, each t, *J*=6 Hz, 4-H), 3.66, 3.98 (total 2H, each t, *J*=6 Hz, 3-H), 7.09-7.21 (2H, m, 6-H and 7-H), 7.33 (1H, d, *J*=8 Hz, 8-H), 7.48 (1H, d, *J*=8 Hz, 5-H), 7.85 (1H, br s, Ar-NH), 8.26, 8.40 (total 1H, s, CHO). ^{13}C-NMR: 21.0 (C4), 24.0 (C3' and C4'), 36.8 (C3), 38.7 (C2'and C5'), 67.0 (C1), 109.9 (C4a), 111.1 (C8), 118.2 (C7), 119.8 (C5), 122.2 (C6), 126.7 (C4b), 135.5 (C9a), 136.0 (C8a), 160.4 (CHO). LR-EIMS (*m/z*): 254 (M^+), 184 (base peak). *Anal*. Calcd for $C_{16}H_{18}N_2O$: C, 75.39; H, 7.15; N, 10.75. Found: C, 75.56; H, 7.13; N, 11.01.

2-Formyl-1,2,3,4-tetrahydro-β-carboline-1-spirocyclohexane (11g) (112 mg, 9%) was obtained from **8** (1.00 g, 6 mmol) and **2g** (0.54 g, 5.2 mmol) as colorless plates recrystallized from MeOH-hexane, mp:280-281℃. IR: 1627, 1508. ^{1}H-NMR: 1.40-1.99 (8H, m, 3'-H, 4'-H, 5'-H and 6'-H), 2.36 (2H, d, *J*=15 Hz, 2'-H), 2.79-2.84 (2H, m, 4-H), 3.97-4.02 (2H, m, 3-H), 7.07-7.20 (2H, m, 6-H and 7-H), 7.33 (1H, d, *J*=8 Hz, 8-H), 7.47 (1H, d, *J*=8 Hz, 5-H), 7.85 (1H, br s, Ar-NH), 8.64 (total 1H, s, CHO). ^{13}C-NMR: 19.7 (C3' and C5'), 25.0 (C4), 27.4 (C4'), 37.8 (C2' and C6'), 47.4 (C4), 57.7 (C1), 111.0 (C8), 112.8 (C4a), 119.6 (C7), 120.5 (C_5), 121.7 (C6), 131.5 (C4b), 135.3 (C9a), 136.2 (C8a), 161.1 (CHO). RL-EIMS (*m/z*): 268 (M^+), 184 (base peak). *Anal*. Calcd for $C_{17}H_{20}N_2O$: C, 75.79; H, 7.48; N, 10.14. Found: C, 76.09; H, 7.51; N, 10.44.

2-Formyl-1,2,3,4-tetrahydro-β-carboline-1-spiro-1'-(2',3'-dihydro-1*H*-indene) (11h) (282 mg, 24%) was obtained from **8** (1.00 g, 6 mmol) and **2h** (0.69 g, 5.2 mmol) as colorless plates recrystallized from MeOH-hexane, mp: 180-181℃. IR: 1653. ^{1}H-NMR: 2.56, 2.61 (total 1H, each t, *J*=8 Hz, 3'-H), 2.62, 2.67 (total 1H, each t, *J*=8 Hz, 3'-H), 2.94, 2.96 (total 1H, each t, *J*=3 Hz, 4-H), 3.10, 3.70 (total 3H, each dd, *J*=5, 12 Hz, 3-H and 4-H), 3.18, 3.24 (total 1H, each dd, *J*=3, 8 Hz, 2'-H), 4.90, 4.94 (total 1H, each q, *J*=3 Hz, 2'-H), 7.0-7.6 (8H, m, Ph), 7.96, 8.10 (1H, s, CHO). ^{13}C-NMR: 21.0 (C4), 29.8 (C3'), 37.0 (C2'), 40.9 (C3), 69.2 (C1), 110.7 (C4a), 111.0 (C8), 118.5 (C7), 119.8 (C5), 122.4 (C6), 125.4 (C5'), 125.9 (C6'), 126.5 (C4b), 128.0 (C4'), 129.9 (C7'), 135.6 (C3a' or C7a'), 136.3 (C3a' or C7a'), 141.0 (C9a), 145.5 (C8a), 161.2 (CHO). LR-EIMS (*m/z*): 302 (M^+), 244 (base peak). HR-EIMS *m/z* (M^+): Calcd for $C_{15}H_{18}N_2$: 302.1437. Found: 302.1431.

Synthesis of 1,1-Disubstituted 1,2,3,4-Tetrahydro-β-carbolines (13) Typical procedure: A mixture of **8** (1.00 g, 6 mmol), **2a** (0.62 g, 5.2 mmol) and Ti(O-*i*Pr)$_4$ (2.22 g, 7.8 mmol) was heated at 80°C for 3 h under an argon atmosphere. To the reaction mixture was added a mixture of CF_3COOH (59.3 g, 0.52 mol) and trifluoroacetic anhydride (1.1 g, 5.2 mmol) at 0°C, then the mixture was heated at 70°C for 3 h. The reaction mixture was diluted with MeOH (100 mL) and passed through a short SiO_2 column ($CHCl_3$-MeOH) to remove TiO_2. The eluent was concentrated *in vacuo* to *ca*. 50 mL and the residue was extracted with $CHCl_3$. After removal of the solvent of extract *in vacuo*, the residue was purified by chromatography over Al_2O_3 (AcOEt-hexane (1:1)) to give **13a** (1.35 g, 99%).

1-Methyl-1-phenyl-1,2,3,4-tetrahydro-β-carboline (13a) A pale brown solid. (HCl salt: colorless prisms recrystallized from MeOH-Et_2O, mp: 273-275°C (decomp), (lit., [6] mp: 267-269°C)). IR: 3397, 2929, 1490. ^{1}H-NMR: 1.83 (3H, s, CH_3), 2.2-3.2 (4H, m, 3-H and 4-H), 7.1-7.3 (9H, m, 5-H, 6-H, 7-H, 8-H and PhH), 7.78 (1H, br s, Ar-N<u>H</u>). ^{13}C-NMR: 22.7 (C4), 28.2 (CH_3), 39.7 (C3), 56.8 (C1), 109.7 (C4a), 110.8 (C8), 118.4 (C7), 119.4 (C5), 121.8 (C6), 126.8 (Ph-CHx2), 127.2 (Ph-CH), 127.3 (C4b), 128.2(Ph-CHx2), 135.7 (C9a), 138.1 (C8a), 146.2 (Ph-C). LR-EIMS (*m/z*): 262 (M^+), 247(base peak).

HR-EIMS *m/z* (M^+): Calcd for $C_{18}H_{18}N_2$: 262.1469. Found: 262.1449.

1,1-Dimethyl-1,2,3,4-tetrahydro-β-carboline (13b) (0.95 g, 91%) was obtained from **8** (1.00 g, 6.3 mmol) and **2b** (0.38 g, 5.2 mmol) as pale yellow plates crystallized from Et_2O-hexane, mp: 110-113°C (lit.,[7] mp 140-141°C (recrystallized from cyclohexane)) . IR: 3399. ^{1}H-NMR: 1.47 (6H, s, CH_3x2), 2.72 (2H, t, *J*=6 Hz, 4-H), 3.21 (2H, t, *J*=6 Hz, 3-H), 7.1-7.2 (2H, m, 6-H and 7-H), 7.30 (1H, d, *J*=8 Hz, 5-H), 7.47 (1H, d, *J*=8 Hz, 8-H), 7.75 (1H, br s, Ar-N<u>H</u>). ^{13}C-NMR: 22.8 (C4), 28.8 (CH_3x2), 39.6 (C3), 50.4 (C1), 107.2 (C4a), 110.6 (C8), 118.1 (C7), 119.1 (C5), 121.3 (C6), 127.2 (C4b), 135.4 (C9a), 140.2 (C8a). LR-EIMS (*m/z*): 200 (M^+), 57 (base peak). HR-EIMS *m/z* (M^+): Calcd for $C_{13}H_{16}N_2$: 200.1314. Found: 200.1327.

1-Ethyl-1-methyl-1,2,3,4-tetrahydro-β-carboline (13c) (1.04 g, 91%) was obtained from **8** (1.00 g, 6.3 mmol) and **2c** (0.38 g, 5.2 mmol)as a pale yellow gum. IR: 3199. ^{1}H-NMR: 0.89 (3H, t, *J*=8 Hz, CH_2-C<u>H</u>$_3$), 1.42 (3H, s, CH_3), 1.7-1.9 (2H, m, C<u>H</u>$_2$-CH_3), 2.69-2.73 (2H, m, 4-H), 3.1-3.3 (2H, m, 3-H), 7.1-7.5 (4H, m, 5-H, 6-H, 7-H, 8-H), 7.69 (1H, br s, Ar-N<u>H</u>). ^{13}C-NMR: 8.2 (CH_2-<u>C</u>H_3), 22.9 (C4), 26.7 (CH_3), 33.8 (<u>C</u>H_2-CH_3), 39.6 (C3), 53.3 (C1), 108.4 (C4a), 110.6 (C8), 118.0 (C7), 119.1 (C5), 121.3 (C6), 127.3 (C4b), 135.5 (C9a), 140.0 (C8a). LR-EIMS (*m/z*): 214 (M^+), 185 (base peak). HR-EIMS *m/z* (M^+): Calcd for $C_{14}H_{18}N_2$: 214.1457. Found: 214.1467.

1-Methyl-1-phenylsulfanyl-1,2,3,4-tetrahydro-β-carboline (13d) (1.06 g, 69%) was obtained from **8** (1.00 g, 6.3 mmol) and **2d** (0.86 g, 5.2 mmol) as a pale yellow gum. IR: 1581. ^{1}H-NMR: 1.46 (3H, s, CH_3), 1.85 (brs s, 2-H), 2.67 (2H, t, *J*=6 Hz, 4-H), 3.08-3.12 (2H, m, 3-H), 3.23 (1H, d, *J*=13 Hz, CH_2S), 3.40 (1H, d, *J*=13 Hz, CH_2S), 7.0-7.3 (9H, m, 5-H, 6-H, 7-H, 8-H and PhH), 7.89 (1H, br s, Ar-N<u>H</u>). ^{13}C-NMR: 22.8 (C4), 26.9 (CH3), 39.7 (CH_2S), 46.2 (C3), 53.9 (C1), 109.2 (C4a), 110.9 (C8), 118.3 (C7), 119.4 (C5), 121.8 (C6), 126.4 (Ph-CH), 127.0 (C4b), 128.9 (Ph-CHx2), 129.9 (Ph-CHx2), 135.6 (C9a), 136.5 (Ph-C), 137.7 (C8a). CIMS (*m/z*): 309 (MH^+), 89 (base peak).

1,1-Diphenyl-1,2,3,4-tetrahydro-β-carboline (13e) (0.95 g, 57%) was obtained from **8** (1.00 g, 6.2

mmol) and **2e** (0.96 g, 5.2 mmol) as a pale yellow gum. IR: 1617. ^{1}H-NMR: 3.11 (2H, t, *J*=7 Hz, 4-H), 3.69 (2H, t, *J*=7 Hz, 3-H), 7.0-7.8 (14H, m, 5-H, 6-H, 7-H, 8-H and PhHx2), 7.94 (1H, br s, Ar-NH). ^{13}C-NMR: 26.9 (C4), 54.5 (C3), 54.5 (C1), 110.9 (C8), 114.0 (C4a), 118.8 (C7), 121.9 (C5), 122.1 (C6), 127.5 (C4b), 127.6 (Ph-CHx2), 128.0 (Ph-CHx2), 128.1 (Ph-CH), 128.2 (Ph-CHx2), 128.3 (Ph-CHx2), 129.8 (Ph-CH), 136.0 (C9a), 136.6 (C8a), 139.8 (Ph-Cx2). LR-EIMS (*m/z*): 324 (M^+), 130 (base peak). HR-EIMS *m/z* (M^+): Calcd for $C_{23}H_{20}N_2$: 324.1585. Found: 324.1605

1,2,3,4-Tetrahydro-β-carboline-1-spirocyclopentane (13f) (0.84 g, 72%) was obtained from **8** (1.00 g, 6.2 mmol) and **2f** (0.44 g, 5.2 mmol) as colorless plates recrystallized from AcOEt-hexane, mp: 112-115°C (lit.,[8] mp 138-140°C). IR: 1560. ^{1}H-NMR: 1.8-2.0 (8H, m, 2'-H, 3'-H, 4'-H and 5'-H), 2.72 (2H, t, *J*=6 Hz, 4-H), 3.17 (2H, t, *J*=6 Hz, 3-H), 7.1-7.5 (4H, m, 5-H, 6-H, 7-H and 8-H), 7.65 (1H, brs, Ar-NH). ^{13}C-NMR: 22.8 (C4), 24.7 (C3' and C4'), 40.1 (C2' and C5'), 40.5 (C3), 61.7 (C1), 108.5 (C4a), 110.5 (C8), 117.9 (C7), 119.1 (C5), 121.3 (C6), 127.3 (C4b), 135.5 (C9a), 139.2 (C8a). LR-EIMS (*m/z*): 226 (M^+), 197 (base peak). HR-EIMS *m/z* (M^+): Calcd for $C_{15}H_{18}N_2$: 226.1467. Found: 226.1449.

1,2,3,4-Tetrahydro-β-carboline-1-spirocyclohexane (13g) (0.95 g, 76%) was obtained from **8** (1.00 g, 6.2 mmol) and **2g** (0.54 g, 5.2 mmol) as a colorless plates recrystallized from AcOEt-hexane, mp: 128-130°C (lit.,[8] mp 133-134°C). IR: 3394, 2927. ^{1}H-NMR: 1.6-1.9 (10H, m, 2'-H, 3'-H, 4'-H, 5'-H and 6'-H), 2.69 (2H, t, *J*=6 Hz, 4-H), 3.12 (2H, t, *J*=6 Hz, 3-H), 7.1-7.5 (4H, m, 5-H, 6-H, 7-H and 8-H), 7.70 (1H, br s, Ar-NH). ^{13}C-NMR: 20.6 (C3' and C5'), 22.3 (C4), 25.0 (C4'), 35.8 (C2' and C6'), 38.4 (C3), 51.6 (C1), 107.2 (C4a), 110.0 (C8), 117.4 (C7), 118.5 (C5), 120.6 (C6), 126.8 (C4b), 137.4 (C9a), 140.5 (C8a). LR-EIMS (*m/z*): 240 (M^+), 209 (base peak). HR-EIMS *m/z* (M^+): Calcd for $C_{16}H_{20}N_2$: 240.1634. Found: 240.1630.

1,2,3,4-Tetrahydro-β-caeboline-1-spiro-1'-(2',3'-dihydro-1*H*-indene) (13h) (0.20 g, 14%) was obtained from **8** (1.00 g, 6.2 mmol) and **2h** (0.69 g, 5.2 mmol) as colorless plates recrystallized from ether-hexane, mp: 167-169°C. IR: 3401, 2931. ^{1}H-NMR: 1.2-1.3 (1H, m, 2'-H), 2.3-2.5 (2H, m, one of

2’-H and 3’-H), 2.8-3.3 (5H, m, 3’-H and 3-H, 4-H), 7.0-7.6 (8H, m, 5-H, 6-H, 7-H, 8-H and ArH), 7.69 (1H, br s, Ar-NH). ^{13}C-NMR: 22.8 (C4), 30.0 (C3’), 40.1 (C2’), 40.9 (C3), 65.6 (C1), 110.3 (C4a), 110.8 (C8), 118.2 (C7), 119.3 (C5), 121.7 (C6), 124.1 (C5’), 125.2 (C6’), 126.8 (C4’), 127.3 (C4b), 128.5 (C7’), 135.9 (C9a), 137.5 (C8a), 144.4 (C3a’), 147.0 (C7a’). LR-EIMS (*m/z*): 274 (M^+, base peak). HR-EIMS *m/z* (M^+): Calcd for $C_{19}H_{18}N_2$: 274.1469. Found: 274.1454.

Hydrolysis of 11 . General Procedure: A solution of **11** (0.35 mmol) in EtOH (20 mL) and 20% NaOH (20 mL) was refluxed for 18 h. The reaction mixture was concentrated *in vacuo*, and the residue was extracted with $CHCl_3$. After removal of the solvent *in vacuo*, the residue was purified by chromatography over SiO_2 (AcOEt-hexane (4:1)) to give **13**. Yields were described as below.

13a (159 mg, 88%) was obtained from **11a** (200 mg, 0.69 mmol). **13b** (169 mg, 96%) was obtained from **11b** (200 mg, 0.88 mmol). **13c** (160 mg, 90%) was obtained from **11d** (200 mg, 0.83 mmol). **13d** (146 mg, 79%) was obtained from **11d** (200 mg, 0.60 mmol). **13f** (158 mg, 89%) was obtained from **11f** (200 mg, 0.79 mmol). **13g** (158 mg, 88%) was obtained from **11g** (200 mg, 0.75 mmol). **13h** (154 mg, 85%) was obtained from **11d** (200 mg, 0.66 mmol).

REFERENCES AND NOTES

1. A. Pictet and T. Spengler, *Ber*., 1911, **44**, 2030.
2. Y. Horiguchi, H. Kodama, M. Nakamura, T. Yoshimura, K. Hanezi, H. Hamada, T. Saitoh, and T. Sano, *Chem. Pharm. Bull*., 2002, **50**, 253.
3. G. Bringmann, C. T. Ewers, and R.Walter, "Comprehensive Organic Synthesis," Vol. 6, ed. by B. M. Trost and I. Fleming, Pergamon Press, Oxford, pp. 736-740, 1991 ; E. D. Cox and J. M. Cook, *Chem. Rev*., 1995, **95**, 1797.
4. The structure of **12b** was determined from spectral analysis of 6-acetyl-1,1-dimethyl-1,2,3,4-tetrahydro-β-carboline which was obtained by hydrolysis of **12b** with HCl.

5. A. Yokoyama, T. Ohwada, and K. Shudo, *J. Org. Chem.*, 1999, **64**, 611.

6. M. Ohkubo, A. Kuno, K. Katsuta, Y. Ueda, K. Shirakawa, H. Nakanishi, T. Kinoshita, and H. Takasugi, *Chem. Pharm. Bull*., **44**, 1996, 778.

6. N. Carrasco, A. Urzua, and B. K. Cassels, *J. Org. Chem*., 1973, **38**, 4342.

8. J. G. Rodriguez and P. Gil-Lopetegui, *J. Heterocycl. Chem*., 1993, **30**, 373.