

Alkylation of 3,4-Dihydro- β -carboline¹⁾

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A new general procedure for the alkylation of the C=N double bond of 3,4-dihydro- β -carboline has been developed with amphiphilic reaction systems such as $\text{BF}_3 \cdot \text{OEt}_2/\text{RLi}$, RMgX , R_2CuLi or trimethylsilyl trifluoromethanesulfonate/ RLi , RMgX to give the corresponding 1-substituted-1,2,3,4-tetrahydro- β -carbolines.

Keywords C=N double bond; alkylation; 1-substituted-1,2,3,4-tetrahydro- β -carboline; 3,4-dihydro- β -carboline; organometallic reagent

Synthesis of amines by nucleophilic addition of organometallic reagents to imines has received increasing attention in recent literature.²⁾ Reduction of a C=N double bond with a hydride reagent to the corresponding amine has been widely used, and several successful reductions of the C=N double bond using chiral hydride reagents have been reported.³⁾ We have recently described the asymmetric reduction of imines with chiral dialkoxyboranes.⁴⁾ However, due to the ease of the formation of metalloenamines and the lower electrophilicity of the C=N double bond compared with the corresponding C=O double bond⁵⁾ less attention has been paid to the reaction of C=N double bonds with carbon nucleophiles. The activation of an imine either by transformation into an iminium salt⁶⁾ or by coordination with Lewis acid⁷⁾ is often necessary for coupling with nucleophiles.

As a part of long-term aim of developing a rational synthetic procedure for preparing amines, we have explored the nucleophilic addition of carbon nucleophiles to imines. In our initial approach to the alkylation of imines with various organometallic reagents, 3,4-dihydro- β -carboline **1** was chosen as a stable imine of particular interest, since a number of biologically active indole alkaloids contain the 1-substituted tetrahydro- β -carboline ring system. In the course of our research on the synthesis of indole alkaloids, we have reported the total synthesis of β -carboline alkaloids such as fumitremorgin B,⁸⁾ fumitremorgin C,⁹⁾ and eudistomins,¹⁰⁾ and have recently reported our study on the Pictet–Spengler reaction,¹¹⁾ which has been widely used for the construction of the tetrahydro- β -carboline skeleton. In

addition, Meyers and co-workers have reported efficient asymmetric alkylations of tetrahydro- β -carboline controlled with a chiral amidine auxiliary.¹²⁾ More recently, several groups have reported the alkylation reaction of 3,4-dihydro- β -carboline (**1**) in syntheses of β -carboline alkaloids.¹³⁾

Herein we report details of our approach to afford a wide range of 1-substituted tetrahydro- β -carbolines by the simple alkylation of readily available **1**¹⁴⁾ with organometallic compounds.

Our initial attempts at alkylation of the C=N double bond of **1** with MeLi, MeMgBr, and Me₂CuLi without any activation of the imine failed and no adduct was obtained, suggesting that the activation of the C=N double bond is

TABLE I. Alkylation of the BF_3 -Iminium Salt **2** with Organolithium Reagents

Run	Nucleophile (molar eq)	Conditions Temperature (°C)	Time (h)	Product (%)
1	MeLi (3)	–23	4	3a 91
2	<i>n</i> -BuLi (3)	–23	4	3b 83
3	<i>sec</i> -BuLi (3)	–23	2	3c 48 ^{a)}
4	<i>tert</i> -BuLi (3)	–23	5	3d 89
5	PhLi (3)	–23	3	3e 75
6	PhC $\equiv$ CLi (5)	–23	6	3f 61
7	LiCH_2CO_2 <i>tert</i> -Bu (5)	–78	5	3g 68
8	LiCH_2CN (5)	–78 (3 h) then room temp. (13 h)		3h 31
9	LiCH_2CN (5)	–23	10	3h 70

a) Mixture of diastereomers.

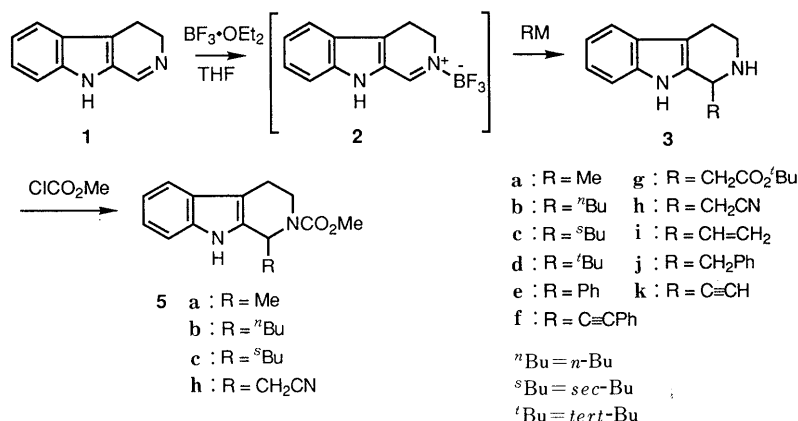


Chart 1

necessary. Thus, we investigated the Lewis acids-mediated addition of various organometallic reagents to **1**.

Method A: Activation by Coordination with $\text{BF}_3 \cdot \text{OEt}_2$ Our first examination of the alkylation **1** was carried out in the presence of $\text{BF}_3 \cdot \text{OEt}_2$. A solution of **1** in tetrahydrofuran (THF) was treated with 1.1 molar eq of $\text{BF}_3 \cdot \text{OEt}_2$ at 0°C to obtain the BF_3 -iminium salt **2**, followed by the addition of MeLi (3 molar eq). The addition of the methyl group to the $\text{C}=\text{N}$ functionality occurred smoothly to give 1-methyltetrahydro- β -carboline **3a** in 91% yield as shown in Table I (Chart 1).

Likewise, other 1-alkyl derivatives **3**¹⁵⁾ were readily obtained in high yields by addition of the corresponding alkyl lithium reagents, although the reaction of **2** with *sec*-BuLi proceeded in lower yield. Tables II and III give the results for the formation of a variety of 1-substituted tetrahydro- β -carbolines **3**¹⁵⁾ using other organometallic

reagents such as Grignard reagents and organocopper reagents. In most cases, lithium reagents gave better yields than Grignard and/or copper reagents. For instance, *tert*-BuLi could be successfully employed, but the use of *tert*-BuMgCl gave low yields of amine. Other Lewis acid mediators, such as TiCl_4 , SnCl_4 , and BH_3 , were also examined with Me_2CuLi , but gave poor results.

Method B: Activation by Transformation into the Trimethylsilyl (TMS)-Iminium Salt In order to improve the alkylation of **1**, a related approach using TMS-iminium salts was examined. Compound **1** was initially deprotonated with 1 molar eq of *n*-BuLi in THF at -78°C and then treated with 2 molar eq of trimethylsilyl trifluoromethanesulfonate to convert it to the TMS-iminium salt **4**.^{13c)} Addition of MeLi (3 molar eq) to **4** thus formed at -78°C effected the formation of **3a**, which was isolated as the carbamate **5a** in 70% yield (Chart 2).

Similar sequential treatment of **1** with other organolithium reagents, including furan and pyrrole derivatives, as well as Grignard reagents led to the smooth formation of the corresponding amine **3** (in some cases isolated as **5**), as depicted in Table IV and V. Other iminium salts, such

TABLE II. Alkylation of the BF_3 -Iminium Salt **2** with Grignard Reagents

Run	Nucleophile (molar eq)	Conditions Temperature ($^\circ\text{C}$)	Time (h)	Product	(%)
1	MeMgBr (3)	-23	4	3a	81
2	<i>n</i> -BuMgCl (3)	-23	4	3b	77
3	<i>tert</i> -BuMgCl (3)	-23	4	3d	19
4	$\text{CH}_2=\text{CHMgBr}$ (5)	-23	2	3i	52
5	PhCH_2MgCl (5)	-23	5	3j	60

TABLE III. Alkylation of the BF_3 -Iminium Salt **2** with Organocopper Reagents

Run	Nucleophile (molar eq)	Conditions Temperature ($^\circ\text{C}$)	Time (h)	Product	(%)
1	Me_2CuLi (3)	-23	0.5	5a	74
2	<i>n</i> -Bu ₂ CuLi (3)	-78	2	5b	83
3	<i>sec</i> -Bu ₂ CuLi (3)	-45	1.5	5c	48 ^{a)}
4	<i>tert</i> -Bu ₂ CuLi (3)	-50	1.5	3d	89
5	$(\text{CH}_2=\text{CH})_2\text{CuMgBr}$ (3)	-42	1	3i	75
6	$(\text{HC}\equiv\text{C})_2\text{CuLi}$ (3)	-78	1	3k	61
7	Ph_2CuLi (3)	-23	1	3e	0

a) Mixture of diastereomers.

TABLE IV. Alkylation of the TMS-Iminium Salt **4** with Organolithium Reagents

Run	Nucleophile (molar eq)	Conditions Temperature ($^\circ\text{C}$)	Time (h)	Product	(%)
1	MeLi (3)	-78	1	5a	70
2	<i>n</i> -BuLi (3)	-78	4	5b	80
3	<i>sec</i> -BuLi (3)	-78	2	5c	37 ^{a)}
4	<i>tert</i> -BuLi (3)	-78	5	5d	34
5	PhLi (3)	-78	3	3e	72
6	$\text{HC}\equiv\text{CLi}$ (3)	-23 (1 h) then room temp. (0.3 h)		3k	47
7	$\text{PhC}\equiv\text{CLi}$ (3)	-23	1	3f	59
8	PhCH_2Li (3)	-78	2	3j	46
9	Li-  (5)	-23	1	5l	16
10	Li-  (5)	-23	1	5m	29

a) Mixture of diastereomers.

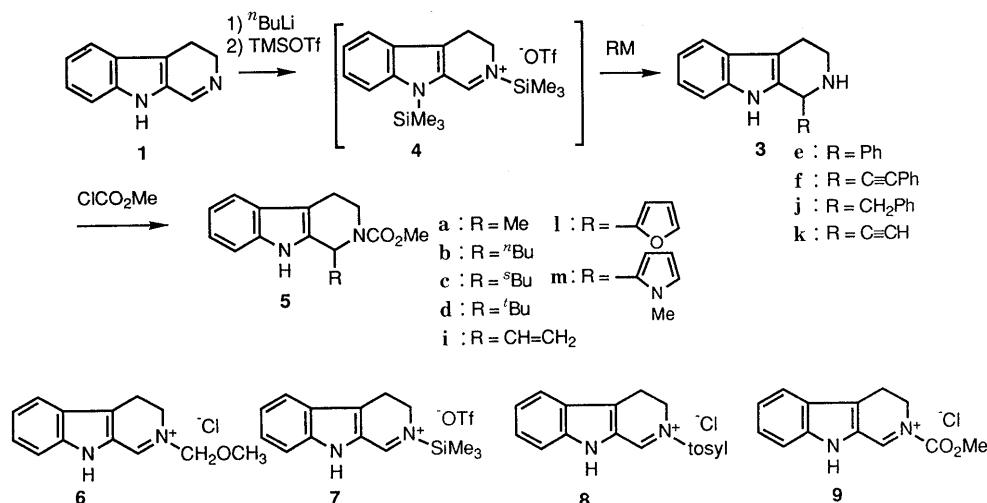


Chart 2

TABLE V. Alkylation of the TMS-Iminium Salt **4** with Grignard Reagents

Run	Nucleophile (molar eq)	Conditions Temperature (°C)	Time (h)	Product	(%)
1	MeMgBr (3)	-42	1	5a	71
2	<i>n</i> -BuMgCl (3)	-42	1	5b	80
3	<i>tert</i> -BuMgCl (3)	-78	1	5d	10
4	PhMgBr (3)	-42	1.5	3e	71
5	CH ₂ =CHMgBr (3)	-23	1.5	5i	52
6	HC≡CMgBr (3)	-23 (1 h) then room temp. (1 h)		3k	60

as the *N*_b-methoxymethyl derivative **6** and *N*_b-trimethylsilyl derivative **7**, prepared *in situ*, were treated with Me₂CuLi, but these gave less satisfactory results, affording **3a** in 17% and 47% yields, respectively. Other reactions attempted using the *N*_b-tosyl derivative **8** and *N*_b-methoxycarbonyl salt **9** with Me₂CuLi failed.

One advantage of this method over the Pictet–Spengler reaction is that 1-vinyl- and 1-ethynyltetrahydro-β-carbolines **3i** and **3k** are readily accessible, albeit in moderate yields, because these compounds are inaccessible or are obtained in quite low yields *via* the conventional Pictet–Spengler reaction due to the instability of the requisite unsaturated aldehydes toward acids.

In conclusion, the alkylation reaction described herein proceeds in high yield and represents one of the few methods currently available for efficiently adding an alkyl group, particularly acetylenic, vinyl, furyl, and pyrrolyl groups, to the azomethine functionality of **1**. This methodology provides a potentially useful strategy for preparing important intermediates for the synthesis of various amines, including indole alkaloids.¹⁶⁾

Further studies on the extension of this methodology to asymmetric systems and application to the synthesis of natural products are in progress.

Experimental

Melting points were determined with Yamato MP-1 and Yanagimoto micro melting point instruments and are uncorrected. UV spectra were recorded on a Hitachi 323 spectrophotometer and refer to a solution in 95% EtOH (λ in nm). Infrared (IR) spectra (ν in cm⁻¹) were obtained with a Hitachi 260-10 spectrophotometer. Unless otherwise noted, IR spectra refer to KBr disks. Mass spectra (MS) were recorded on a Hitachi M-60, RMU-7, JEOL HX-110, or JMS-AM20 mass spectrometer. Proton and carbon nuclear magnetic resonance (¹H- and ¹³C-NMR) spectra were recorded on JEOL JNM-FX-270, GX-270, GSX-400, JNM-GSX-500, and JNM-GSX-500A apparatus. NMR spectra were measured in CDCl₃ and chemical shifts were recorded in δ values (ppm) relative to Me₄Si internal standard. Microanalyses were performed on a Perkin-Elmer 240 C, H, N analyzer. Silica gel column chromatography was performed on Fuji-Davison BW-200 or BW-300 silica gel.

Alkylation of the BF₃-Iminium Salt **2 of 3,4-Dihydro-β-carboline** Method A: General Procedure: BF₃·OEt₂ (0.27 ml, 2.2 mmol) was added to a solution of 3,4-dihydro-β-carboline (**1**) (340 mg, 2 mmol) in THF (20 ml) at -23°C. The mixture was stirred for 5 min at the same temperature, then MeLi (1.1 M solution in Et₂O, 5.5 ml, 6.1 mmol) was added and the whole was stirred for 4 h at -23°C. Then 10% aqueous NaOH (5 ml) was added and the mixture was extracted with CH₂Cl₂. The combined organic layers were washed with brine and dried over Na₂SO₄, and the solvent was evaporated *in vacuo*. The residue was chromatographed on silica gel column (AcOEt: MeOH) to give 1-methyl-1,2,3,4-tetrahydro-β-carboline (**3a**) (339 mg, 91%) as a pale yellow solid.

Alkylation of the TMS-Iminium Salt **4 of 3,4-Dihydro-β-carboline** Method B: General Procedure: *n*-BuLi (1.59 M in hexane, 0.66 ml, 1.00 mmol) was added to a stirred solution of 3,4-dihydro-β-carboline (**1**) (170 mg, 1

mmol) in THF (8 ml) at -23°C under an argon atmosphere. After the mixture has been stirred for 20 min at -23°C, trimethylsilyl trifluoromethanesulfonate (0.43 ml, 2.20 mmol) was added. The resulting mixture was then cooled to -78°C, and a 1.00 M ethereal solution of MeLi (3.0 ml, 3.0 mmol) was added *via* a syringe. The reaction mixture was stirred for 2 h at -78°C, then the reaction was quenched with 50% aqueous AcOH (10 ml) and the resulting mixture stirred vigorously at room temperature for 1 h. The mixture was diluted with CH₂Cl₂ and basified with K₂CO₃ and aqueous NaHCO₃. To this solution, an excess of ClCO₂Me was added under ice-cooling and stirring was continued for a short time. After reaction was deemed to be complete (checked by TLC), the organic layer was separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The residue was chromatographed on a silica gel column (AcOEt:hexane) to give 1-methyl-2-methoxycarbonyl-1,2,3,4-tetrahydro-β-carboline (**5a**) (179 mg, 70%) as a colorless amorphous solid.

1-Methyl-1,2,3,4-tetrahydro-β-carboline (3a**)** Orange prisms, mp 178.0–179.0°C (AcOEt) (lit. mp 179–180°C¹⁷⁾). UV λ_{max} nm: 224, 275sh, 283, 290. IR ν_{max}: 3290, 1450, 740 cm⁻¹. ¹H-NMR (500 MHz) δ: 1.46 (3H, d, *J* = 6.8 Hz, Me), 1.58 (1H, brs, N_b-H), 2.72 (1H, dddd, *J* = 1.7, 3.4, 5.1, 15.4 Hz, 4-H_a), 2.78 (1H, dddd, *J* = 2.0, 5.3, 9.0, 15.4 Hz, 4-H_b), 3.06 (1H, ddd, *J* = 5.1, 9.0, 13.1 Hz, 3-H_a), 3.37 (1H, ddd, *J* = 3.4, 5.4, 13.0 Hz, 3-H_b), 4.19 (1H, tq, *J* = 2.0, 6.8 Hz, 1-H), 7.09 (1H, dt, *J* = 1.0, 7.9 Hz, aromatic), 7.15 (1H, dt, *J* = 1.2, 8.0 Hz, aromatic), 7.31 (1H, dd, *J* = 1.0, 8.0 Hz, aromatic), 7.48 (1H, d, *J* = 7.8 Hz, aromatic), 7.75 (1H, brs, N_a-H). MS *m/z* (%): 186 (M⁺, 66.8), 185 (M⁺ - 1, 32.0), 171 (100), 157 (58.0), 156 (49.2).

1-Butyl-1,2,3,4-tetrahydro-β-carboline (3b**)** Pale brown oil. UV λ_{max} nm: 226, 274, 283, 290. IR ν_{max} (neat): 3400, 1460, 1450, 740 cm⁻¹. ¹H-NMR (500 MHz) δ: 0.94 (3H, t, *J* = 7.14 Hz, 4'-Me), 1.35–1.55 (4H, m, 2'-H_a, 3'-H₂, N_b-H), 1.64–1.71 (2H, m, 1'-H_a, 2'-H_b), 1.87 (1H, m, 1'-H_b), 2.70–2.80 (2H, m, 4-H₂), 3.03 (1H, ddd, *J* = 5.23, 8.52, 12.92 Hz, 3-H_a), 3.36 (1H, ddd, *J* = 3.85, 4.95, 12.93 Hz, 3-H_b), 4.06 (1H, m, 1-H), 7.09 (1H, dt, *J* = 1.10, 7.70 Hz, aromatic), 7.14 (1H, dt, *J* = 1.10, 7.97 Hz, aromatic), 7.31 (1H, td, *J* = 0.83, 7.79 Hz, aromatic), 7.48 (1H, d, *J* = 7.70 Hz, aromatic), 7.75 (1H, brs, N_a-H). ¹³C-NMR (67.8 MHz) δ: 14.05 (q, Me), 22.75 (t, 4), 22.95 (t, 3'), 28.08 (t, 2'), 34.79 (t, 1'), 42.63 (t, 3), 52.70 (d, 1), 108.91 (s, 4a), 110.68 (d, 8), 118.02 (d, 5), 119.29 (d, 6), 121.39 (d, 7), 127.58 (s, 4b), 135.65 (s, 9a), 136.44 (s, 8a). FAB-MS *m/z* (%): 229 (MH⁺, 100), 171 (M⁺ - Bu, 88.16). Exact FAB-MS Calcd for C₁₅H₂₀N₂ + H: 229.1706. Found: 229.1709.

1-sec-Butyl-1,2,3,4-tetrahydro-β-carboline (3c**) (Mixture of Diastereomers)** Pale brown caramel. UV λ_{max} nm: 227, 275sh, 283, 291. The diastereomeric ratio was about 1:1, from the signal integral ratios in the ¹H-NMR spectrum. Integral ratio of ¹H-NMR (500 MHz): 1'-Me, δ 0.81 (d, *J* = 6.8 Hz, less polar isomer): δ 1.10 (d, *J* = 6.8 Hz, more polar isomer) = 1.00:1.02; 4'-Me, δ 1.03 (t, *J* = 7.5 Hz, less polar isomer): δ 0.91 (t, *J* = 7.3 Hz, more polar isomer) = 1.06:1.00.

1-sec-Butyl-1,2,3,4-tetrahydro-β-carboline (3c**) (Less Polar Isomer)** Pale brown caramel. UV λ_{max} nm: 227, 275sh, 283, 291. ¹H-NMR (500 MHz) δ: 0.84 (3H, d, *J* = 6.87 Hz, Me), 1.03 (3H, t, *J* = 7.42 Hz, Me), 1.42–1.51 (1H, m, MeCH_a), 1.61–1.69 (1H, m, MeCH_b), 1.88–2.10 (2H, m, 1-CH and N_b-H, exchangeable (1H)), 2.70–2.80 (2H, m, 4-H₂), 2.99 (1H, ddd, *J* = 4.67, 10.18, 12.65 Hz, 3-H_a), 3.44 (1H, ddd, *J* = 2.47, 4.85, 12.37 Hz, 3-H_b), 4.19 (1H, brs, 1-H), 7.08–7.16 (2H, m, aromatic), 7.31–7.33 (1H, m, aromatic), 7.49 (1H, d, *J* = 7.69 Hz, aromatic), 7.73 (1H, brs, N_a-H, exchangeable). MS *m/z* (%): 228 (M⁺, 2.95), 171 (M⁺ - sec-Bu, 100). Exact-MS Calcd for C₁₅H₂₀N₂: 228.1628. Found: 228.1615.

1-sec-Butyl-1,2,3,4-tetrahydro-β-carboline (3c**) (More Polar Isomer)** Pale brown caramel. UV λ_{max} nm: 228, 275sh, 283, 291. ¹H-NMR (500 MHz) δ: 0.92 (3H, t, *J* = 7.42 Hz, Me), 1.11 (3H, d, *J* = 6.87 Hz, Me), 1.19–1.28 (1H, m, MeCH_a), 1.37–1.45 (1H, m, MeCH_b), 1.84–1.91 (2H, m, 1-CH and N_b-H, exchangeable (1H)), 2.70–2.76 (2H, m, 4-H₂), 2.98 (1H, ddd, *J* = 5.22, 9.34, 12.64 Hz, 3-H_a), 3.40 (1H, ddd, *J* = 3.30, 5.22, 12.65 Hz, 3-H_b), 4.09 (1H, m, 1-H), 7.08–7.17 (2H, m, aromatic), 7.32 (1H, dd, *J* = 0.82, 7.98 Hz, aromatic), 7.49 (1H, d, *J* = 7.70 Hz, aromatic), 7.73 (1H, brs, N_a-H, exchangeable). MS *m/z* (%): 228 (M⁺, 3.22), 171 (M⁺ - sec-Bu, 100). Exact-MS Calcd for C₁₅H₂₀N₂: 228.1628. Found: 228.1613.

1-tert-Butyl-1,2,3,4-tetrahydro-β-carboline (3d**)** Pale brown prisms, mp 94.5–95.5°C (AcOEt). UV λ_{max} nm: 226, 275sh, 283, 291. IR ν_{max}: 3250, 1460, 1440, 800, 740 cm⁻¹. ¹H-NMR (500 MHz) δ: 1.11 (9H, s, *tert*-Bu), 1.69 (1H, brs, N_b-H), 2.71 (2H, m, 4-H₂), 2.90 (1H, m, 3-H_a), 3.37 (1H, ddd, *J* = 3.9, 4.2, 12.2 Hz, 3-H_b), 3.85 (1H, s, 1-H), 7.09 (1H, dt, *J* = 1.1,

7.8 Hz, aromatic), 7.14 (1H, dt, $J=1.2$, 8.3 Hz, aromatic), 7.31 (1H, d, $J=8.1$ Hz, aromatic), 7.49 (1H, d, $J=7.6$ Hz, aromatic), 7.81 (1H, brs, N_a -H). FAB-MS m/z (%): 229 (NH^+ , 57.08), 171 ($M^+ - \text{tert-Bu}$, 100). Anal. Calcd for $C_{15}H_{20}N_2$: C, 78.90; H, 8.83; N, 12.27. Found: C, 78.88; H, 8.57; N, 12.10.

1-Phenyl-1,2,3,4-tetrahydro- β -carboline (3e) Light yellow prisms, mp 166.0–167.0 °C (AcOEt–hexane) [lit. mp 168–169 °C¹⁸]; mp 167–168 °C¹⁹). UV λ_{max} nm: 226, 275, 283, 290. IR ν_{max} : 3400, 3250, 1455, 750 cm^{-1} . $^1\text{H-NMR}$ (500 MHz) δ : 1.73 (1H, brs, N_b -H), 2.88 (1H, dddd, $J=1.7$, 3.9, 4.7, 15.4 Hz, 4- H_a), 2.92 (1H, dddd, $J=1.9$, 5.4, 9.0, 15.4 Hz, 4- H_b), 3.14 (1H, ddd, $J=4.7$, 9.1, 12.5 Hz, 3- H_a), 3.38 (1H, ddd, $J=3.9$, 5.4, 12.7 Hz, 3- H_b), 5.16 (1H, brt, 1-H), 7.12 (2H, m, aromatic), 7.21 (1H, m, aromatic), 7.30–7.38 (5H, m, aromatic), 7.50–7.56 (2H, m, aromatic and N_a -H). MS m/z (%): 249 ($M^+ + 1$, 18.43), 248 (M^+ , 100), 218 (82.91), 171 (48.77).

1-(2'-Phenylethynyl)-1,2,3,4-tetrahydro- β -carboline (3f) Pale yellow needles, mp 139.5–140.5 °C (AcOEt). UV λ_{max} nm: 226, 240sh, 250sh, 273, 283, 291. IR ν_{max} : 3370, 3120, 2300sh, 1620, 740, 685 cm^{-1} . $^1\text{H-NMR}$ (500 MHz) δ : 1.58 (1H, brs, N_b -H), 2.81 (2H, m, 4- H_2), 3.17 (1H, ddd, $J=5.4$, 6.9, 12.7 Hz, 3- H_a), 3.47 (1H, t, $J=5.4$, 12.7 Hz, 3- H_b), 5.21 (1H, s, 1-H), 7.12 (1H, dt, $J=0.8$, 7.9 Hz, aromatic), 7.18 (1H, dt, $J=1.0$, 8.0 Hz, aromatic), 7.31 (3H, m, Ph), 7.35 (1H, dd, $J=0.5$, 7.9 Hz, aromatic), 7.44 (2H, dd, $J=1.7$, 7.6 Hz, Ph), 7.51 (1H, d, $J=7.6$ Hz, aromatic), 8.01 (1H, brs, N_a -H). $^{13}\text{C-NMR}$ (125 MHz) δ : 22.13 (t, 4), 42.12 (t, 3), 45.25 (d, 1), 84.03 (s, $C\equiv C$), 87.74 (s, $C\equiv C$), 108.90 (s, 4a), 111.05 (d, Ph), 118.34 (d, aromatic), 119.49 (d, aromatic), 121.99 (d, aromatic), 122.44 (s, Ph), 127.30 (s, 4b), 128.31 (d, Ph), 128.51 (d, aromatic), 131.44 (s, 9a), 131.48 (d, Ph), 135.79 (s, 8a). FAB-MS m/z (%): 273 (MH^+ , 77.54), 272 (M^+ , 100), 271 (58.47), 244 (40.58). Anal. Calcd for $C_{19}H_{16}N_2$: C, 83.79; H, 5.92; N, 10.29. Found: C, 83.91; H, 5.86; N, 9.99.

1-tert-Butoxycarbonylmethyl-1,2,3,4-tetrahydro- β -carboline (3g) Light brown prisms, mp 138.5–140.0 °C (AcOEt). UV λ_{max} nm: 226, 274, 283.5, 291. IR ν_{max} : 3350, 3280, 1720, 1710sh, 1155, 750 cm^{-1} . $^1\text{H-NMR}$ (500 MHz) δ : 1.49 (9H, s, *tert*-Bu), 1.74 (1H, brs, N_b -H, exchangeable), 2.75 (4H, m, 4- H_2 and CH_2CO), 3.10 (1H, ddd, $J=5.4$, 6.8, 12.2 Hz, 3- H_a), 3.25 (1H, t, $J=5.1$, 12.9 Hz, 3- H_b), 4.44 (1H, m, 1-H), 7.08 (1H, dt, $J=1.2$, 8.0 Hz, 6-H), 7.15 (1H, dt, $J=1.2$, 8.0 Hz, 7-H), 7.32 (1H, d, $J=8.0$ Hz, 8-H), 7.49 (1H, dd, $J=0.5$, 7.8 Hz, 5-H), 8.62 (1H, brs, N_a -H, exchangeable). $^{13}\text{C-NMR}$ (125 MHz) δ : 22.62 (t, 4), 28.08 (q, Me), 42.07 (t, CH_2CO), 42.19 (t, 3), 48.94 (d, 1), 81.58 (s, $OCMe_3$), 108.83 (s, 4a), 110.91 (d, 8), 118.05 (d, 5), 119.20 (d, 6), 121.60 (d, 7), 127.13 (s, 4b), 135.31 (s, 9a), 135.44 (s, 8a), 172.62 (s, $C=O$). MS m/z (%): 286 (M^+ , 11.76), 229 ($M^+ - \text{tert-Bu}$, 13.77), 171 ($M^+ - CH_2CO\text{tert-Bu}$, 100). Anal. Calcd for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.74; N, 9.78. Found: C, 71.00; H, 7.57; N, 9.50.

1-Cyanomethyl-1,2,3,4-tetrahydro- β -carboline (3h) Brown caramel. UV λ_{max} nm: 222, 273, 281, 290sh. IR ν_{max} : 3400–3100 br, 2340, 2250, 2180, 1450, 740 cm^{-1} . $^1\text{H-NMR}$ (270 MHz) δ : 2.34 (1H, brs, N_b -H), 2.65–2.81 (2H, m, 4- H_2), 2.75 (2H, d, $J=6.9$ Hz, CH_2CN), 3.07–3.22 (2H, m, 3- H_2), 4.36 (1H, t, $J=6.9$ Hz, 1-H), 7.07–7.13 (1H, m, aromatic), 7.18 (1H, dt, $J=1.31$, 7.25 Hz, aromatic), 7.33 (1H, d, $J=7.91$ Hz, aromatic), 7.49 (1H, d, $J=7.25$ Hz, aromatic), 8.32 (1H, brs, N_a -H). MS m/z (%): 211 (M^+ , 13.62), 171 ($M^+ - CH_2CN$, 100).

1-Vinyl-1,2,3,4-tetrahydro- β -carboline (3i) Light yellow prisms, mp 137.5–138.5 °C (CH_2Cl_2). UV λ_{max} nm: 226, 275sh, 283, 291.5. IR ν_{max} : 3280, 1445, 920, 740 cm^{-1} . $^1\text{H-NMR}$ (500 MHz) δ : 1.83 (1H, brs, N_b -H), 2.72–2.85 (2H, m, 4- H_2), 3.10 (1H, ddd, $J=4.95$, 8.25, 12.37 Hz, 3- H_a), 3.35 (1H, t, $J=4.67$, 12.37 Hz, 3- H_b), 4.61 (1H, d, $J=7.97$ Hz, 1-H), 5.30 (1H, ddd, $J=0.55$, 1.65, 10.17 Hz, vinyl-H), 5.38 (1H, ddd, $J=0.82$, 1.37, 17.04 Hz, vinyl-H), 5.98 (1H, ddd, $J=7.97$, 10.17, 17.05 Hz, vinyl-H), 7.10 (1H, dt, $J=1.10$, 7.70 Hz, aromatic), 7.15 (1H, dt, $J=1.10$, 7.97 Hz, aromatic), 7.30 (1H, t, $J=0.83$, 7.98 Hz, aromatic), 7.50 (1H, dd, $J=0.55$, 7.70 Hz, aromatic), 7.72 (1H, brs, N_a -H). $^{13}\text{C-NMR}$ (125 MHz) δ : 22.34 (t, 4), 42.07 (t, 3), 56.43 (d, 1), 108.97 (s, 4a), 110.78 (d, aromatic), 117.06 (t, vinyl- CH_2), 118.17 (d, aromatic), 119.26 (d, aromatic), 121.57 (d, aromatic), 127.53 (s, 4b), 133.51 (s, 9a), 135.75 (s, 8a), 138.37 (d, vinyl-CH). FAB-MS m/z (%): 199 (MH^+ , 96.55), 198 (M^+ , 100), 171 (25.13), 170 (27.73), 169 (25.07). Anal. Calcd for $C_{13}H_{14}N_2$: C, 78.75; H, 7.12; N, 14.13. Found: C, 78.53; H, 6.96; N, 13.86.

1-Benzyl-1,2,3,4-tetrahydro- β -carboline (3j) Yellow prisms, mp 121.5–122.5 °C (AcOEt–hexane). UV λ_{max} nm: 225, 274sh, 283.5, 291. IR ν_{max} : 3140, 3050, 1100, 745, 700 cm^{-1} . $^1\text{H-NMR}$ (500 MHz) δ : 1.83 (1H, brs, N_b -H), 2.69–2.81 (2H, m, 4- H_2), 3.00–3.13 (3H, m, 3- H_a and $PhCH_2$), 3.33 (1H, t, $J=4.67$, 12.37 Hz, 3- H_b), 4.37 (1H, t, $J=7.15$ Hz, 1-H), 7.08 (1H, dt, $J=1.10$, 7.70 Hz, aromatic), 7.12 (1H, dt, $J=1.10$, 7.15 Hz,

aromatic), 7.18–7.38 (7H, m, aromatic and N_a -H), 7.48 (1H, d, $J=7.69$ Hz, aromatic). $^{13}\text{C-NMR}$ (125 MHz) δ : 22.63 (t, 4), 41.64 (t, CH_2Ph), 42.38 (t, 3), 53.98 (d, 1), 109.28 (s, 4a), 110.70 (d, aromatic), 118.08 (d, aromatic), 119.28 (d, aromatic), 121.50 (d, aromatic), 126.88 (d, Ph), 127.21 (s, 4b), 128.81 (d, Ph), 129.31 (d, Ph), 135.46 (s, 9a), 135.56 (s, 8a), 138.13 (s, Ph). FAB-MS m/z (%): 263 (MH^+ , 66.60), 171 ($M^+ - CH_2Ph$, 100). Anal. Calcd for $C_{18}H_{18}N_2$: C, 82.41; H, 6.92; N, 10.68. Found: C, 82.21; H, 6.76; N, 10.38.

1-Ethynyl-1,2,3,4-tetrahydro- β -carboline (3k) Brown caramel. UV λ_{max} nm: 225, 275, 283, 290.5. IR ν_{max} : 3250, 2110, 1450, 740 cm^{-1} . $^1\text{H-NMR}$ (500 MHz) δ : 1.88 (1H, brs, N_b -H), 2.34 (1H, d, $J=2.4$ Hz, $C\equiv CH$), 2.77 (2H, m, 4- H_2), 3.13 (1H, ddd, $J=5.3$, 6.6, 13.0 Hz, 3- H_a), 3.41 (1H, t, $J=5.5$, 12.9 Hz, 3- H_b), 4.97 (1H, dd, $J=1.7$, 3.9 Hz, 1-H), 7.11 (1H, ddd, $J=1.0$, 7.1, 7.8 Hz, aromatic), 7.18 (1H, ddd, $J=1.2$, 7.0, 8.1 Hz, aromatic), 7.33 (1H, t, $J=1.0$, 7.1 Hz, aromatic), 7.49 (1H, d, $J=7.7$ Hz, aromatic), 8.01 (1H, brs, N_a -H). $^{13}\text{C-NMR}$ (125 MHz) δ : 22.07 (t, 4), 42.03 (t, 3), 44.52 (d, 1), 72.19 (d, $C\equiv CH$), 82.54 (s, $C\equiv CH$), 109.18 (s, 4a), 110.98 (d, aromatic), 118.38 (d, aromatic), 119.59 (d, aromatic), 122.13 (d, aromatic), 127.27 (s, 4b), 130.85 (s, 9a), 135.77 (s, 8a). MS m/z (%): 196 (M^+ , 60.2), 167 (100). Exact-MS Calcd for $C_{13}H_{12}N_2$: 196.1002. Found: 196.1000.

2-Methoxycarbonyl-1-methyl-1,2,3,4-tetrahydro- β -carboline (5a) Pale yellow prisms, mp 160.0–160.5 °C (AcOEt). UV λ_{max} nm: 225, 273sh, 282sh, 290. IR ν_{max} : 3280, 2950, 1670 cm^{-1} . $^1\text{H-NMR}$ (500 MHz) δ : 1.50 (3H, d, $J=6.6$ Hz, Me), 2.73 (1H, m, 4- H_a), 2.81 (1H, brs, 4- H_b), 3.20 (1H, brs, 3- H_a), 3.78 (3H, s, OMe), 4.35 (3/5H, brs, 3- H_b), 4.51 (2/5H, brs, 3- H_b), 5.25 (2/5H, brs, 1-H), 5.39 (3/5H, brs, 1-H), 7.09 (1H, m, aromatic), 7.15 (1H, m, aromatic), 7.31 (1H, dd, $J=0.82$, 7.97 Hz, aromatic), 7.47 (1H, d, $J=7.7$ Hz, aromatic), 7.81 (2/5H, brs, NH), 8.05 (3/5H, brs, NH). MS m/z (%): 244 (M^+ , 34), 229 ($M^+ - Me$, 100). Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.67; H, 6.70; N, 11.15.

1-Butyl-2-methoxycarbonyl-1,2,3,4-tetrahydro- β -carboline (5b) Colorless prisms, mp 158.0–158.5 °C (AcOEt). UV λ_{max} nm: 225, 273sh, 282, 290. IR ν_{max} : 3280, 2940, 1670 cm^{-1} . $^1\text{H-NMR}$ (500 MHz) δ : 0.92 (3H, d, $J=6.9$ Hz, Me), 1.30–1.45 (4H, m, $CH_2 \times 2$), 1.80 (2H, m, CH_2), 2.69 (1H, brs, 4- H_a), 2.82 (1H, brs, 4- H_b), 3.22 (1H, brs, 3- H_a), 3.74 and 3.76 (total 3H, each s, OMe), 4.32 (3/5H, brs, 3- H_b), 4.52 (2/5H, brs, 3- H_b), 5.17 (2/5H, brs, 1-H), 5.32 (3/5H, brs, 1-H), 7.09 (1H, m, aromatic), 7.15 (1H, m, aromatic), 7.31 (1H, d, $J=8.0$ Hz, aromatic), 7.45 (1H, brs, aromatic), 7.78 (2/5H, brs, NH), 7.92 (3/5H, brs, NH). MS m/z (%): 286 (M^+ , 12), 229 ($M^+ - Bu$, 100). Anal. Calcd for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.74; N, 9.78. Found: C, 71.47; H, 7.77; N, 9.75.

1-sec-Butyl-2-methoxycarbonyl-1,2,3,4-tetrahydro- β -carboline (5c) (Mixture of Diastereomers) Colorless prisms. UV λ_{max} nm: 226, 275sh, 283, 290.5. IR ν_{max} : 3280, 2950, 1670, 735 cm^{-1} . $^1\text{H-NMR}$ (500 MHz, at 50 °C) δ : 0.94 (t, $J=7.6$ Hz, Me), 0.99 (t, $J=7.6$ Hz, Me), 1.09 (d, $J=6.8$ Hz, Me) (total 6H for Me), 1.20–1.40 (1H, m, $MeCH_2$), 1.50–1.80 (1H, m, $MeCH_2$), 1.91 (1H, m, $MeCH_2$), 2.70 (1H, dd, $J=4.4$, 15.3 Hz, 4- H_a), 2.84 (1H, brd, 4- H_b), 3.28 (1H, brd, 3- H_a), 3.72 (3H, s, OMe), 4.30–4.60 (1H, br, 3- H_b), 4.90–5.20 (1H, br, 1-H), 7.08 (1H, t, $J=7.2$ Hz, aromatic), 7.15 (1H, m, aromatic), 7.30 (1H, d, $J=8.0$ Hz, aromatic), 7.46 (1H, d, $J=7.8$ Hz, aromatic), 7.72 (1H, brd, N_a -H). MS m/z (%): 287 ($M^+ + 1$, 0.51), 286 (M^+ , 5.97), 229 ($M^+ - \text{sec-Bu}$, 100).

1-tert-Butyl-2-methoxycarbonyl-1,2,3,4-tetrahydro- β -carboline (5d) Colorless prisms, mp 207.0–209.0 °C (AcOEt–hexane). UV λ_{max} nm: 226, 274sh, 283, 291. IR ν_{max} : 3330, 2970, 1680, 1240, 745 cm^{-1} . $^1\text{H-NMR}$ (500 MHz) δ : 1.09 and 1.13 (total 9H, each s, *tert*-Bu, at 55 °C; δ 1.12 (s)), 2.68–2.85 (2H, m, 4- H_2), 3.36–3.50 (1H, m, 3- H_a), 3.71 and 3.73 (total 3H, each s, OMe, at 55 °C; δ 3.72 (s)), 4.40 (5/9H, m, 3- H_b), 4.60 (4/9H, m, 3- H_b), 4.99 (4/9H, brs, 1-H), 5.17 (5/9H, brs, 1-H), 7.08–7.19 (2H, m, aromatic, at 55 °C; δ 7.08 (1H, dt, $J=0.92$, 7.42 Hz) and 7.15 (1H, dt, $J=1.28$, 7.60 Hz)), 7.32 (1H, m, aromatic, at 55 °C; δ 7.30 (td, $J=0.73$, 8.06 Hz)), 7.48 (1H, m, aromatic, at 55 °C; δ 7.46 (d, $J=7.51$ Hz)), 7.76 (4/9H, brs, N_a -H, at 55 °C; δ 7.74 (brs)), 7.83 (5/9H, brs, N_a -H, at 55 °C; δ 7.74 (brs)). FAB-MS m/z (%): 287 (MH^+ , 39.54), 229 ($M^+ - \text{tert-Bu}$, 100). Anal. Calcd for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.74; N, 9.78. Found: C, 71.62; H, 7.53; N, 9.76.

1-Cyanomethyl-2-methoxycarbonyl-1,2,3,4-tetrahydro- β -carboline (5h) Pale green prisms, mp 163.5–165.0 °C (AcOEt). UV λ_{max} nm: 224, 275, 283sh, 290.5. IR ν_{max} : 3350, 2240, 1680, 760, 740 cm^{-1} . $^1\text{H-NMR}$ (500 MHz) δ : 2.77–2.96 (4H, m, 4- H_2 and CH_2CN), 3.15 (3/7H, brt, 3- H_a), 3.28 (4/7H, brt, 3- H_a), 3.81 (3H, s, OMe), 4.40 (4/7H, brd, $J=7.44$ Hz, 3- H_b), 4.59 (3/7H, brd, 3- H_b), 5.52 (3/7H, brs, 1-H), 5.61 (4/7H, brs, 1-H), 7.13 (1H, t, $J=7.69$ Hz, aromatic), 7.22 (1H, t,

$J = 7.42$ Hz, aromatic), 7.37 (1H, d, $J = 8.25$ Hz, aromatic), 7.50 (1H, d, $J = 7.70$ Hz, aromatic), 8.19 (3/7H, brs, N_a -H), 8.26 (4/7H, brs, N_a -H). FAB-MS m/z (%): 270 (M^+ , 41.98), 269 (M^+ , 51.35), 229 (100). Anal. Calcd for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.60. Found: C, 66.62; H, 5.47; N, 15.59.

2-Methoxycarbonyl-1-vinyl-1,2,3,4-tetrahydro- β -carboline (5i) Pale yellow prisms, mp 122.0–123.0 °C (CH_2Cl_2). UV λ_{max} nm: 225, 274sh, 282, 290.5. IR ν_{max} : 3280, 1680, 1410, 990, 900, 740 cm^{-1} . 1H -NMR (500 MHz, at 55 °C) δ : 2.72 (1H, ddd, $J = 1.10, 4.12, 15.40$ Hz, 4- H_a), 2.85 (1H, dddd, $J = 1.65, 5.50, 11.82, 15.40$ Hz, 4- H_b), 3.18 (1H, dt, $J = 4.12, 12.09$ Hz, 3- H_a), 3.76 (3H, s, OMe), 4.39 (1H, brs, 3- H_b), 5.22 (1H, td, $J = 1.10, 17.04$ Hz, vinyl-H), 5.27 (1H, td, $J = 1.10, 10.17$ Hz, vinyl-H), 5.71 (1H, brs, 1-H), 6.02 (1H, ddd, $J = 6.32, 10.17, 17.05$ Hz, vinyl-H), 7.09 (1H, ddd, $J = 0.82, 7.15, 7.98$ Hz, aromatic), 7.16 (1H, ddd, $J = 1.10, 7.15, 8.25$ Hz, aromatic), 7.30 (1H, td, $J = 0.83, 7.97$ Hz, aromatic), 7.48 (1H, d, $J = 7.97$ Hz, aromatic), 7.73 (1H, brs, N_a -H). FAB-MS m/z (%): 257 (M^+ , 100), 229 ($M^+ - CH = CH_2$). Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.02; H, 6.21; N, 10.74.

1-(2-Furyl)-2-methoxycarbonyl-1,2,3,4-tetrahydro- β -carboline (5l) Pale yellow prisms, mp 167.0–168.5 °C (AcOEt–hexane). UV λ_{max} nm: 224, 276sh, 282, 291. 1H -NMR (400 MHz) δ : 2.28 (1/2H, d, $J = 3.29$ Hz, 4- H_a), 2.76 (1/2H, d, $J = 3.11$ Hz, 4- H_b), 2.91 (1H, m, 4- H_b), 3.30 (1H, m, 3- H_a), 3.78 (3H, s, OMe), 4.36 (1/2H, m, 3- H_b), 4.53 (1/2H, m, 3- H_b), 6.17 (1H, brs, 1-H), 6.31 (3/2H, dd, $J = 1.83, 3.11$ Hz, furyl-3' and 4'-H), 6.51 (1/2H, m, furyl-3'-H), 7.38 (1H, dd, $J = 0.73, 1.83$ Hz, furyl-5'-H), 7.10–7.53 (4H, m, aromatic), 7.92 (1H, brs, NH, exchangeable). MS m/z (%): 296 (M^+ , 100), 237 ($M^+ - COOMe$, 42.0).

2-Methoxycarbonyl-1-(*N*-methyl-2-pyrrolyl)-1,2,3,4-tetrahydro- β -carboline (5m) Pale yellow prisms, mp 192.0–193.5 °C (AcOEt–hexane). UV λ_{max} nm: 224, 276sh, 282, 291. 1H -NMR (400 MHz) δ : 2.73 (1H, dd-like, 4- H_a), 2.94 (1H, m, 4- H_b), 3.29 (1H, dt-like, 3- H_a), 3.76 (6H, brs, OMe and NMe), 4.12 (1H, m, 3- H_b), 5.67 (1H, brs, pyrrolyl-3'-H), 5.97 (1H, d, $J = 2.47$ Hz, pyrrolyl-4'-H), 6.53 (1H, brs, 1-H), 6.65 (1H, d, $J = 1.93$ Hz, pyrrolyl-5'-H), 7.10–7.52 (4H, m, aromatic), 7.79 (1H, brs, NH, exchangeable). MS m/z (%): 310 ($M^+ + 1$, 21.4), 309 (M^+ , 100), 250 ($M^+ - COOMe$, 26.1).

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