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Simple and efficient synthesis of tetrahydro-β-carbolines *via* the Pictet–Spengler reaction in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP)†

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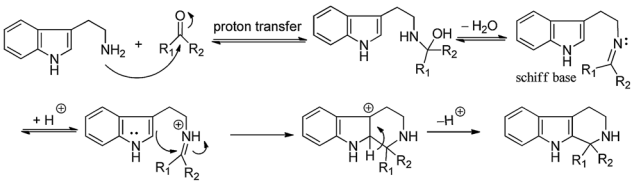
1,1,1,3,3,3-Hexafluoro-2-propanol (HFIP) can act as both the solvent and the catalyst to promote the Pictet–Spengler reactions between tryptamine derivatives and aldehydes or activated ketones. For most substrates, removing the low boiling point HFIP by distillation directly afforded tetrahydro-β-carbolines in high yields.

Introduction

Tetrahydro-β-carboline is an important structural unit present in many bioactive natural products such as Fumitremorgin C and Neonaucleoside A and C.[1] The heterocyclic compounds containing this structural unit have been found to exhibit a broad spectrum of biological activities such as antiviral and antitumor activities.[2] The Pictet–Spengler reaction is the most effective method for the direct synthesis of tetrahydro-β-carbolines and therefore has attracted much attention from synthetic organic chemists.[3] The Pictet–Spengler reaction involves two steps.[3c] The first step is the formation of the imine intermediate (Schiff base) through the dehydration reaction of an electron-rich β-arylethylamine with an aldehyde or a ketone in the presence of an acidic catalyst. Then the imine intermediate undergoes a 6-*endo*-trig cyclization, which is also catalyzed by an acidic catalyst (Scheme 1).



Scheme 1 The mechanism and the catalysts of the Pictet–Spengler reaction. R_1, R_2 = H, alkyl, aryl; catalysts: Brøsted acid: TFA, AcOH, HCl, TfOH, *p*-TsOH, HCOOH, perfluorooctanesulfonic acid, $Cl_2CHCOOH$, $BrCH_2COOH$, *etc.*; Lewis acid: $Yb(OTf)_3$, $Sc(OTf)_3$, $AuCl_3$/AgOTf, $Ca(HFIP)_2$, *etc.*

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According to the mechanism of the Pictet–Spengler reaction, only when an appropriate amount of Brønsted acid catalyst is used, the reaction can afford product in optimal chemical yield. If a largely excessive amount of Brønsted acid catalyst is used, the starting amine may be protonated and loses its nucleophilicity. Moreover, in some cases, strong acidic conditions are incompatible with acid-labile aldehydes. However, when the amount of the Brønsted acid catalyst is insufficient, consequently the imine is not properly activated and the addition reaction would be very slow. The frequently used Brønsted acids are trifluoroacetic acid,[4a–c] acetic acid,[4d–f] hydrochloric acid,[4h] trifluoromethanesulfonic acid,[4i] *p*-toluenesulfonic acid,[4j] and formic acid.[4g,k] In recent years, Lewis acids[5] and some other miscellaneous reagents[6] have also been applied to catalyze the Pictet–Spengler reaction. In 2003, Ganesan's research group reported that the reaction could be catalyzed by a variety of Lewis acids. Among them, $Yb(OTf)_3$ was shown to be highly effective with the assistance of microwave irradiation.[5a] In 2006, Youn's group utilized $AuCl_3$/AgOTf as the catalyst to promote the Pictet–Spengler reaction, but the imine should be prepared in advance.[5b] Although several Brønsted acid catalysts are capable of mediating the transformation, the kind and the amount of the acid, as well as the solvent and the temperature of the reaction should be carefully optimized in order to obtain a high chemical yield for a given substrate.[4c] The screening process inevitably results in a waste of reaction substrates and heavy labor work. For most of the Lewis acid-catalyzed Pictet–Spengler reactions, the reactions take rather long reaction time and microwave irradiation is applied to enhance the reactivity.[5a] Also, the usage of Brønsted acid or Lewis acid catalysts generates waste salt or poisonous metal ion which are harmful to the environment. Therefore, performing the Pictet–Spengler reaction with a recyclable catalyst and under a mild reaction condition is still highly desirable.

Fluorinated alcohols possess various special properties:[7] high polarity (polarity (E_N^T): HFIP = 1.068, EtOH = 0.654), high ionizing power (ionizing power (Y): HFIP = 3.82, EtOH = −1.75),

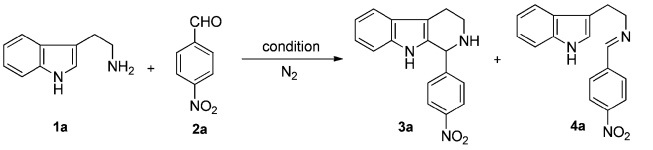
but with very weak nucleophilicity (nucleophilicity (N): HFIP = −4.23, EtOH = 0). The weak acidic property of HFIP (HFIP: pK_a = 9.3, EtOH: pK_a = 15.9) makes it can act as both the solvent and the catalyst. In recent years, many reports showed that HFIP could promote a variety of reactions without additional acid catalyst.[8] In 2010, our group reported that HFIP could efficiently promote the electrophilic aromatic substitutions between arenes and epoxides with high regio- and stereo-control.[9] Although HFIP is a relatively expensive organic solvent, it can be easily recovered by distillation after the completion of reactions due to its low boiling point (bp = 58.6 °C) and low viscosity.

In the year of 2005, Professor Zhu's research group observed that LiCl in the mixed solvent of toluene and HFIP (v:v = 4 : 1) could promote the Pictet–Spengler reaction between an amine and ethyl glyoxylate at room temperature. The authors also observed that without the addition of LiCl, the reaction could take place at 85 °C but give a substantially low yield of the desired product.[10] In 2007, Saito and Hanzawa reported that the addition of small amount of HFIP (11.5 v/v%) could considerable accelerate the reactions between amine carbamates and aldehydes when the reactions were catalyzed by perfluorooctanesulfonic acid (20 mol% in H_2O).[4l,m] The reaction in dry HFIP proceeded even fast than that in water but the sole use of HFIP at room temperature did not afford the desired product. Here, we report that in refluxing HFIP and without additional catalyst, tryptamine derivatives and aldehydes could dehydrate to the imine intermediates *in situ* and further react to afford the cyclization products tetrahydro-β-carbolines. The HFIP-promoted Pictet–Spengler reactions could avoid the usage of Brønsted acids or Lewis acids and HFIP could be recovered and reused.

Results and discussion

Our previous studies showed that HFIP presented stronger catalytic effect at raised temperature. At room temperature in HFIP, the reaction of tryptamine (**1a**) and *p*-nitrobenzaldehyde (**2a**) proceeded slowly and 99% yield of the cyclized product **3a** was obtained after 12 h (entry 1, Table 1). But in HFIP under refluxing condition, the same reaction provided 99% yield of **3a** within 1 h (entry 2, the same reaction catalyzed by 10% TFA at room temperature gave 72% yield of **3a** after 36 h,[4a] or catalyzed by 1.05 equiv. of HCl at 20 °C under 5 kbar gave 91% yield of **3a** after 1 h (ref. 4h)). After the completion of the reaction, HFIP was distilled off and the residue was the crude product in nearly quantitative yield.[11] Up to 20% volume percent of water in HFIP could be tolerated but the reactions were slower compared with that in pure HFIP (entry 3 and 4). As the amount of water increased to 50% of volume percent, the yield of **3a** decreased and the reaction gave imine **4a** as the major product (entry 5). In pure water under refluxing condition, the reaction gave the imine **4a** in 100% yield (entry 6). We also examined this reaction in several other polar organic solvents having relatively high boiling points (entry 7–11). When the Pictet–Spengler reaction was carried out in refluxing 1,1,1-trifluoroethanol (TFE), the reaction majorly afforded imine **4a** and only 4% yield of **3a** was formed after 24 h. In CH_3CN, DMF, CH_3OH, or *i*-PrOH, the reactions afforded **4a** in quantitative yields judging by the ^{1}H NMR spectra of the crude products.

Table 1 The Pictet–Spengler reactions in HFIP and other solvents without additional catalyst[a]

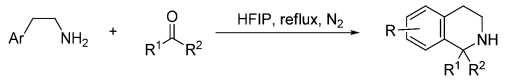


Entry	Solvent	Temperature (°C)	Time (h)	Yield (%) 3a[b]	4a[c]
1	HFIP	r.t.	12	99	0
2	HFIP	Reflux (58.6 °C)	1	99	0
3	H_2O–HFIP (1 : 9)	Reflux	19	98	0
4	H_2O–HFIP (1 : 4)	70	24	94	0
5	H_2O–HFIP (1 : 1)	70	24	16	80
6	H_2O	Reflux	24	0	100
7	TFE	Reflux	24	4	94
8	CH_3CN	Reflux	24	0	100
9	DMF	100	24	0	100
10	CH_3OH	Reflux	24	0	100
11	*i*-PrOH	Reflux	24	0	100

[a] Reaction conditions: the reactions were performed with tryptamine (0.5 mmol) and aldehyde (0.5 mmol) in solvent (0.8 mL). [b] Isolated yield. [c] Yield was determined from the ^{1}H NMR spectrum of the crude product.

In refluxing HFIP, tryptamine (**1a**) could react with a variety of aromatic or aliphatic aldehydes or ketones effectively.[12] As shown in Table 2, for aromatic aldehydes, regardless of electron-withdrawing or electron-donating substituents on the aromatic ring, the reactions could give the tetrahydro-β-carboline products in excellent yields (compounds **3a–3e**, entry 1–5, Table 2). 1-Naphthaldehyde and 2-thenaldehyde also showed excellent reactivities and the chemical yields of compounds **3f** and **3g** were 95% and 91%, respectively (entry 6 and 7). Aliphatic aldehydes required longer reaction time but still gave high chemical yields (compounds **3h–3j**, entry 8–10). Compared with aldehydes, ketones are less reactive and there were fewer literatures reporting the Pictet–Spengler reactions between ketones and tryptamine and the reactions often did not proceed well.[13] The Pictet–Spengler reactions between tryptamine and ketones were also attempted in refluxing HFIP. The trifluoromethyl group in trifluoroacetophenone enhances the activity of the carbonyl group and the reaction in refluxing HFIP provided product **3k** in 76% yield after 24 h (entry 11). Similarly, the reaction of tryptamine with ethyl pyruvate gave product **3l** in 84% yield after 36 h (entry 12). *p*-Nitroacetophenone did not react well, the desired product **3m** was obtained in 21% yield and the imine (43% yield) was formed as the major product (entry 13). The reaction of **1d** with ethyl acetoacetate gave **3n** and the imine in 28% and 68% yields, respectively (entry 14). We also examined the Pictet–Spengler reactions between *p*-nitrobenzaldehyde **2a** and 3-hydroxytyramine (dopamine) **1b** or 3-hydroxy-4-methoxy phenethylamine **1c** in refluxing

Table 2 HFIP-promoted Pictet–Spengler reactions between amines and aldehydes or ketones



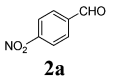
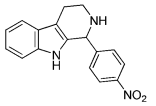
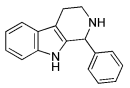
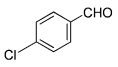
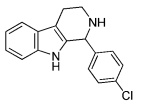
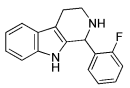
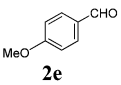
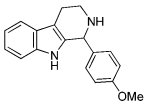
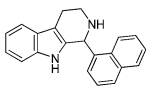
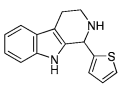
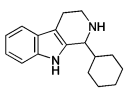
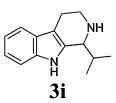
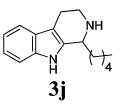
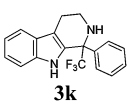
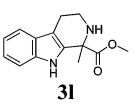
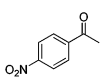
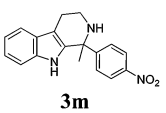
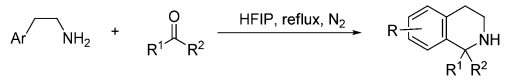
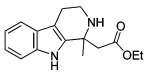
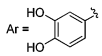
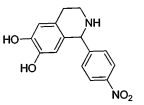
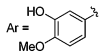
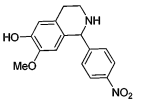
Entry	Amine	Aldehydes or ketones	Product	Time (h)	Yield[a] (%)
1	 **1a**	 **2a**	 **3a**	1	99[b]
2	**1a**	 **2b**	 **3b**	3	93[b]
3	**1a**	 **2c**	 **3c**	2	93[b]
4	**1a**	 **2d**	 **3d**	12	98[b]
5	**1a**	 **2e**	 **3e**	24	91[c]
6	**1a**	 **2f**	 **3f**	24	95[c]
7	**1a**	 **2g**	 **3g**	24	91[c]
8	**1a**	 **2h**	 **3h**	48	83[c] (92)[e]
9	**1a**	 **2i**	 **3i**	16	94[d]
10	**1a**	 **2j**	 **3j**	30	81[d] (93)[e]
11	**1a**	 **2k**	 **3k**	24	76[d] (90)[e]
12	**1a**	 **2l**	 **3l**	36	84[d] (92)[e]
13	**1a**	 **2m**	 **3m**	48	21[d] (67)[e]

Table 2 (*Contd.*)



Entry	Amine	Aldehydes or ketones	Product	Time (h)	Yield[a] (%)
14	**1a**	 **2n**	 **3n**	72	28[d] (100)[e]
15	 **1b**	**2a**	 **3o**	8	93[b]
16	 **1c**	**2a**	 **3p**	6	91[b]

[a] Isolated yield. [b] The reactions were performed with amine (0.5 mmol) and aldehyde (0.5 mmol) in HFIP (0.8 mL) under refluxing condition. [c] The reactions were performed with tryptamine (0.5 mmol) and aldehyde (0.6 mmol) in HFIP (0.8 mL) under refluxing condition. [d] The reactions were performed with tryptamine (0.5 mmol) and carbonyl compounds (0.75 mmol) in HFIP (0.8 mL) under refluxing condition. [e] Conversion of tryptamine.

HFIP.[5c,6g] The reactions gave corresponding tetrahydroisoquinoline derivatives **3o** and **3p** in 93% and 91% yields, respectively (entry 15 and 16). A large-scale Pictet–Spengler reaction was also performed in HFIP. Refluxing benzylaldehyde (31 mmol, 3.3 g, 3.17 mL) and tryptamine (31 mmol, 5 g) in HFIP (15 mL) for 8 h gave the corresponding tetrahydro-β-carboline **3b** in 95% isolated yield.

The previous work from Cook's research group has shown that owing to the high electrophilicity of the imine generated from L-tryptophan methyl ester (**1d**), the Pictet–Spengler reactions between **1d** and aldehydes can proceed in benzene under refluxing condition. These catalyst-free reactions give tetrahydro-β-carbolines with higher chemical yields than those catalyzed by acid catalysts in protic solvents.[6d,k] We further examined the Pictet–Spengler reactions between L-tryptophan methyl ester (**1d**) and aldehydes in refluxing HFIP (Table 3). Refluxing **1d** and *p*-nitrobenzaldehyde in HFIP for 3.5 h gave *cis*/*trans* diastereoisomers of **3q** in 98% isolated yield. The ratio of *cis*- and *trans*- isomer was 52 : 48, which was parallel with those reported in the literatures (entry 1, Table 3).[6d,k] This reaction could also proceed slowly at room temperature and the ratio of the *cis*- and *trans*- isomer obtained was 55 : 45 (entry 2). The reaction between **1d** and other aromatic aldehydes or aliphatic aldehydes were also tested in refluxing HFIP. These reactions all gave very high yields of tetrahydro-β-carbolines (in mixed *cis*- and *trans*- diastereoisomers, entry 3–9). It was worth noting that the Pictet–Spengler reaction between **1d** and salicylaldehyde (**2p**) only give the corresponding imine in refluxing benzene owing to the electron-donating phenolic oxygen on the benzene ring.[6d] However, in refluxing HFIP, this reaction could provide 96% yield of desired tetrahydro-β-carboline **3u** in 12 hours (entry 6).

The HFIP-promoted Pictet–Spengler reactions may be explained from several aspects. The weak acidity of HFIP could activate the carbonyl group to form the imine intermediate, which was also activated by HFIP through the following 6-*endo*-trig cyclization reaction.[8d]

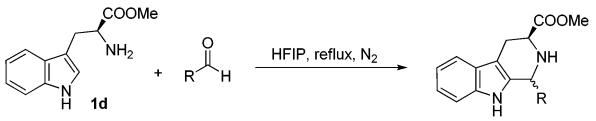
Conclusion

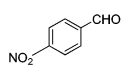
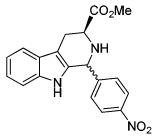
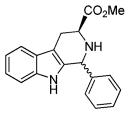
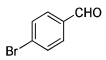
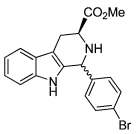
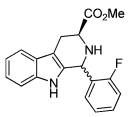
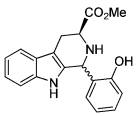
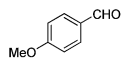
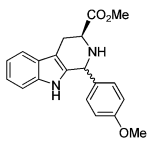
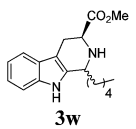
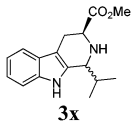
In conclusion, utilizing HFIP as the solvent and also the catalyst under none strictly anhydrous conditions, the Pictet–Spengler reactions between tryptamine derivatives and aldehydes or activated ketones could afford tetrahydro-β-carbolines in high yields. For most of the substrates, the one-pot reactions did not need the work-up procedure. Removing solvent HFIP by distillation directly gave the product pure enough for most of further transformations. HFIP could be recovered and reused, thus no waste salt was generated in the reaction. The simplicity and the environmental benign feature of this method ensure its future application in organic synthesis.

Experimental section

Experimental Details: HFIP was distilled from K_2CO_3 to get rid of possible HF contaminates. All of the reactions were carried out under nitrogen atmosphere. The ^1H NMR spectra were recorded on a 400 MHz NMR machine and ^{13}C NMR spectra were measured on a 100 MHz NMR machine. Peaks recorded are relative to the internal standards: TMS ($\delta = 0.00$) or DMSO-

Table 3 The Pictet–Spengler reactions of L-tryptophan methyl ester and aldehydes[a]



Entry	Aldehydes	Product	Time (h)	Yield[b] (%)	*cis*/*trans*[b]
1	 **2a**	 **3q**	3.5	98	52/48
2[c]	**2a**	**3q**	12	95	55/45
3	 **2b**	 **3r**	6	97	53/47
4	 **2o**	 **3s**	24	93	56/44
5	 **2d**	 **3t**	20	92	48/52
6	 **2p**	 **3u**	12	96	55/45
7	 **2e**	 **3v**	24	87	53/47
8	 **2j**	 **3w**	24	91	55/45
9	 **2i**	 **3x**	20	90	54/46

[a] General procedure: entries 1–7 were performed with L-tryptophan methyl ester (0.5 mmol) and aldehyde (0.6 mmol) in HFIP (0.8 mL) under refluxing condition; entry 8 and 9 were performed with L-tryptophan methyl ester (0.5 mmol) and aldehyde (0.75 mmol) in HFIP (0.8 mL) under refluxing condition. [b] Yields are the isolated yield of the *cis*/*trans* isomers, the *cis*/*trans* ratio was determined by the weight of the isolated product. [c] Room temperature.

d_6 (δ = 2.50) for ^{1}H NMR; $CDCl_3$ (δ = 77.00) or DMSO-d_6 (δ = 39.43) for ^{13}C NMR spectra. High resolution mass spectral analyses (HRMS) were performed on high resolution ESI-FTICR mass spectrometer (Varian 7.0 T). Flash column chromatography were performed with Qingdao–Haiyang® silica gel (200–300 mesh).

General procedure for the preparation of products 3a–3n in Table 2

1-(4-Nitrophenyl)-1,2,3,4-tetrohydro-β-carboline (3a).[4a] (Table 2, entry 1) The starting material of tryptamine **1a** (80 mg, 0.5 mmol) and *p*-nitrobenzaldehyde **2a** (76 mg, 0.5 mmol) were dissolved in HFIP (0.8 mL) under nitrogen atmosphere. The resulting solution was refluxed and monitored by TLC. After completion, HFIP was removed by distillation. The residue was azeotroped with $CHCl_3$ for three times (to get rid of trace amount of HFIP) to afford **3a** (145 mg, 99%) as yellow solid; mp = 172–173 °C (lit.[4a] mp = 172 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, J = 8.8 Hz, 2H), 7.59 (br s, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.48 (d, J = 8.4 Hz, 2H), 7.23–7.26 (m, 1H), 7.11–7.19 (m, 2H), 5.26 (s, 1H), 3.25–3.30 (m, 1H), 3.12–3.19 (m, 1H), 2.89–2.97 (m, 1H), 2.80–2.86 (m, 1H), 1.95 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 149.3, 147.6, 135.9, 132.6, 129.4, 127.1, 123.9, 122.2, 119.7, 118.4, 110.9, 110.8, 57.1, 42.2, 22.3.

1-Phenyl-1,2,3,4-tetrahydro-β-carboline (3b).[4a] Yield 93%; white solid; mp = 162–163 °C (lit.[4a] mp = 160–161 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.53–7.55 (m, 1H), 7.50 (br s, 1H), 7.30–7.39 (m, 5H), 7.21–7.24 (m, 1H), 7.09–7.17 (m, 2H), 5.18 (s, 1H), 3.36–3.42 (m, 1H), 3.12–3.18 (m, 1H), 2.90–2.97 (m, 1H), 2.81–2.86 (m, 1H), 1.82 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 141.5, 135.8, 134.1, 128.6, 128.5, 128.1, 127.1, 121.5, 119.1, 118.0, 110.8, 109.8, 57.7, 42.3, 22.2.

1-(4-Chlorophenyl)-1,2,3,4-tetrahydro-β-carboline (3c).[6e,h] Yield 93%; light yellow solid; mp = 206–207 °C; (lit.[6e] mp = 207–208 °C).^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.57 (d, J = 5.2 Hz, 1H), 7.45 (br s, 1H), 7.34–7.36 (m, 2H), 7.26–7.30 (m, 3H), 7.13–7.20 (m, 2H), 5.18 (s, 1H), 3.37–3.40 (m, 1H), 3.16–3.19 (m, 1H), 2.92–2.95 (m, 1H), 2.82–2.86 (m, 1H), 1.74 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 140.3, 135.8, 133.8, 133.7, 129.8, 128.8, 127.2, 121.8, 119.4, 118.2, 110.8, 110.3, 57.2, 42.4, 22.3.

1-(2-Fluorophenyl)-1,2,3,4-tetrahydro-β-carboline (3d). Yield 98%; light yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.77 (br s, 1H), 7.52–7.54 (m, 1H), 7.25–7.31 (m, 1H), 7.17–7.20 (m, 1H), 7.02–7.14 (m, 5H), 5.54 (s, 1H), 3.24–3.29 (m, 1H), 3.09–3.15 (m, 1H), 2.77–2.91 (m, 2H), 1.94 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.8 (d, J = 245.0 Hz), 135.8, 132.8, 129.9 (d, J = 4.0 Hz), 129.5 (d, J = 8.0 Hz), 128.6 (d, J = 14.0 Hz), 127.1, 124.1 (d, J = 3.0 Hz), 121.6, 119.2, 118.0, 115.5 (d, J = 21.0 Hz), 110.8, 110.4, 50.1 (d, J = 3.0 Hz), 41.6, 22.2; HRMS (ESI) for $C_{17}H_{15}N_2F$: calcd for $[M + H]^+$ m/z 267.1298, found 267.1292.

1-(*p*-Methoxyphenyl)-1,2,3,4-tetrahydro-β-carboline (3e).[6e] Yield 91%; light yellow solid; mp = 203–204 °C (lit.[6e] mp = 205–206 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.68 (br s, 1H), 7.52–7.54 (m, 1H), 7.20 (d, J = 8.8 Hz, 2H), 7.16–7.21 (m, 1H), 7.07–7.14 (m, 2H), 6.85 (d, J = 8.8 Hz, 2H), 5.08 (s, 1H), 3.78 (s, 3H), 3.34–3.37 (m, 1H), 3.07–3.14 (m, 1H), 2.87–2.94 (m, 1H),

2.75–2.83 (m, 1H), 1.95 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.5, 135.8, 134.8, 133.8, 129.6, 127.4, 121.6, 119.3, 118.2, 114.1, 110.8, 110.1, 57.4, 55.3, 42.8, 22.5.

1-(1-Naphthyl)-1,2,3,4-tetrahydro-β-carboline (3f). Yield 95%; white solid; mp = 167–168 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.24 (br s, 1H), 7.88–7.90 (m, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.54–7.60 (m, 2H), 7.46–7.53 (m, 2H), 7.36 (t, J = 7.2 Hz, 1H), 7.25 (br s, 1H), 7.10–7.16 (m, 3H), 5.89 (s, 1H), 3.32–3.35 (m, 1H), 3.14–3.21 (m, 1H), 2.93–3.00 (m, 1H), 2.84–2.91 (m, 1H), 1.96 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 136.8, 135.8, 134.3, 134.1, 131.6, 128.9, 128.7, 127.3, 126.7, 125.8, 125.2, 123.4, 121.6, 119.3, 118.1, 110.8, 110.3, 53.4, 42.5, 22.5; HRMS (ESI) for $C_{21}H_{18}N_2$: calcd for $[M + H]^+$ m/z 299.1548, found 299.1543.

1-(2-Thienyl)-1,2,3,4-tetrahydro-β-carboline (3g).[6i] Yield 91%; light yellow solid; mp = 169–170 °C (lit.[6i] mp = 172–173 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.78 (br s, 1H), 7.53 (d, J = 7.6 Hz, 1H), 7.27 (d, J = 4.8 Hz, 1H), 7.22 (d, J = 8.0 Hz, 1H), 7.08–7.16 (m, 2H), 6.95–7.03 (m, 2H), 5.46 (s, 1H), 3.34–3.39 (m, 1H), 3.11–3.17 (m, 1H), 2.85–2.92 (m, 1H), 2.74–2.81 (m, 1H), 1.99 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 145.8, 135.7, 133.9, 127.3, 126.5, 125.7, 125.7, 121.8, 119.4, 118.4, 110.9, 109.6, 52.9, 42.4, 22.3.

1-Cyclohexyl-1,2,3,4-tetrahydro-β-carboline (3h).[6h,i] Yield 83%; light yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.79 (br, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.32 (d, J = 7.6 Hz, 1H), 7.07–7.16 (m, 2H), 3.96–4.00 (m, 1H), 3.34–3.41 (m, 1H), 2.94–3.03 (m, 1H), 2.65–2.78 (m, 2H), 1.69–1.86 (m, 5H), 1.62 (br s, 1H), 1.47–1.55 (m, 1H), 1.40–1.45 (m, 1H), 1.26–1.37 (m, 1H), 1.10–1.23 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 135.6, 135.3, 127.6, 121.3, 119.2, 117.9, 110.6, 110.0, 57.8, 43.1, 42.3, 30.2, 27.5, 26.8, 26.6, 26.4, 22.8.

1-Isopropyl-1,2,3,4-tetrahydro-β-carboline (3i).[6h,j] Yield 94%; light yellow solid; mp = 117–118 °C; (lit.[6j] mp = 117 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.81 (br s, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.08–7.17 (m, 2H), 4.02–4.05 (m, 1H), 3.39–3.44 (m, 1H), 2.96–3.03 (m, 1H), 2.69–2.78 (m, 3H), 2.16–2.24 (m, 1H), 1.15 (d, J = 6.8 Hz, 3H), 0.89 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 135.7, 134.7, 127.4, 121.6, 119.3, 118.0, 110.7, 110.0, 58.0, 42.9, 31.6, 22.3, 19.4, 17.0.

1-Pentyl-1,2,3,4-tetrahydro-β-carboline (3j).[6i] Yield 81%; light yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.69 (br s, 1H), 7.42 (d, J = 7.6 Hz, 1H), 7.25 (d, J = 8.0 Hz, 1H), 7.01–7.10 (m, 2H), 3.97–4.03 (m, 1H), 3.31 (dt, J = 4.4, 12.8 Hz, 1H), 2.93–3.00 (m, 1H), 2.61–2.74 (m, 2H), 1.76–1.85 (m, 2H), 1.56–1.66 (m, 1H), 1.36–1.52 (m, 2H), 1.22–1.33 (m, 4H), 0.83 (t, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 136.2, 135.5, 127.4, 121.3, 119.2, 117.9, 110.6, 108.7, 52.6, 42.5, 34.9, 32.0, 25.5, 22.6, 22.5, 14.0.

1-Phenyl-1-trifluoromethyl-1,2,3,4-tetrahydro-β-carboline (3k). Yield 76%; white solid; mp = 166–167 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.09 (br s, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.38–7.43 (m, 3H), 7.30–7.35 (m, 3H), 7.26 (t, J = 7.2 Hz, 1H), 7.17 (t, J = 7.6 Hz, 1H), 3.20–3.29 (m, 1H), 2.88–2.96 (m, 2H), 2.71–2.80 (m, 1H), 2.18 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.2, 135.9, 128.7, 128.5, 127.9, 126.5, 126.2 (q, J = 284 Hz), 122.9, 119.8, 118.8, 113.4, 111.2, 64.3 (q, J = 27 Hz), 39.3, 22.0; HRMS (ESI) for $C_{18}H_{15}F_3N_2$: calcd for $[M + H]^+$ m/z 317.1266, found 317.1261.

Methyl-(1-methyl-1,2,3,4-tetrahydro-β-carboline-1-yl) carboxylate (3l). Yield 84%; light yellow solid; mp = 130–132 °C; 1H NMR (400 MHz, CDCl3) δ = 8.26 (br s, 1H), 7.50 (d, J = 7.6 Hz, 1H), 7.35 (d, J = 8.4 Hz, 1H), 7.18 (t, J = 7.2 Hz, 1H), 7.10 (t, J = 7.2 Hz, 1H), 3.78 (s, 3H), 3.21–3.27 (m, 1H), 3.13–3.19 (m, 1H), 2.75–2.83 (m, 1H), 2.67–2.73 (m, 1H), 2.39 (br s, 1H), 1.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.8, 136.0, 132.9, 126.8, 122.2, 119.5, 118.5, 110.9, 110.3, 58.9, 52.8, 40.9, 27.2, 22.2.

1-Methyl-1-(4-nitrophenyl)-1,2,3,4-tetrahydro-β-carboline (3m). Yield 21%; brown liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.10 (d, J = 8.4 Hz, 2H), 7.88 (br s, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.50 (d, J = 8.8 Hz, 2H), 7.38 (d, J = 8.0 Hz, 1H), 7.23 (t, J = 7.6 Hz, 1H), 7.16 (t, J = 7.6 Hz, 1H), 3.16–3.20 (m, 1H), 2.79–2.88 (m, 1H), 2.70–2.77 (m, 2H), 1.83 (s, 3H), 1.72 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 154.0, 146.8, 136.5, 135.8, 127.9, 127.2, 123.3, 122.3, 119.8, 118.6, 111.0, 110.1, 56.8, 39.7, 28.7, 22.6; HRMS (ESI) for $C_{18}H_{17}N_3O_2$: calcd for $[M + H]^+$ m/z 308.1399, found 308.1395.

Ethyl-2-(1-methyl-1,2,3,4-tetrahydro-β-carboline-1-yl) acetate (3n). Yield 28%; brown liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.83 (br s, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.15 (t, J = 7.6 Hz, 1H), 7.08 (t, J = 7.6 Hz, 1H), 4.09–4.20 (m, 2H), 3.14–3.25 (m, 2H), 2.72–2.90 (m, 4H), 1.84 (br s, 1H), 1.60 (s, 3H), 1.22 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.5, 138.1, 135.4, 126.9, 122.7, 119.2, 118.2, 111.0, 108.2, 60.8, 52.0, 45.8, 39.6, 26.6, 22.8, 14.1; HRMS (ESI) for $C_{16}H_{20}N_2O_2$: calcd for $[M + H]^+$ m/z 273.1603, found 273.1602.

General procedure for the preparation of products 3o, 3p in Table 2

1-(4-Nitrophenyl)-1,2,3,4-tetrahydroisoquinoline-6,7-diol (3o).[6g] The hydrochloride salt of 3-hydroxytyramine **1b** (95 mg, 0.5 mmol) and *p*-nitrobenzaldehyde **2a** (76 mg, 0.5 mmol) were dissolved in HFIP (0.8 mL) under nitrogen atmosphere. Pyridine (40 μL, 0.5 mmol) was added to free the amine. The resulting solution was refluxed and monitored by TLC. After completion, the reaction mixture was diluted with CH_2Cl_2 (200 mL). The organic phase was washed with saturated sodium bicarbonate solution, water, brine, and dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: 8% MeOH–dichloromethane) to afford **3o** (133 mg, 93%) as yellow solid; decomposed at 182 °C; (lit.[6g] mp = 210–212 °C (H_2O)). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.71 (br s, 1H), 8.55 (br s, 1H), 8.18 (d, J = 8.8 Hz, 2H), 7.52 (d, J = 8.4 Hz, 2H), 6.49 (s, 1H), 5.97 (s, 1H), 4.97 (s, 1H), 2.96–3.01 (m, 1H), 2.80–2.86 (m, 1H), 2.69–2.76 (m, 1H), 2.52–2.55 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 153.8, 146.4, 143.9, 143.1, 130.0, 127.7, 125.8, 123.1, 115.5, 114.4, 59.8, 41.6, 28.3.

1-(4-Nitrophenyl)-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (3p).[5e] Yield 91%; yellow solid; mp = 157–158 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.86 (br s, 1H), 8.17 (d, J = 8.8 Hz, 2H), 7.51 (d, J = 8.8 Hz, 2H), 6.56 (s, 1H), 6.16 (s, 1H), 5.04 (s, 1H), 3.51 (s, 3H), 2.90–2.95 (m, 1H), 2.80–2.86 (m, 1H), 2.67–2.74 (m, 1H), 2.54–2.60 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 153.6, 146.3, 145.7, 145.1, 129.9, 127.8, 127.3, 123.1, 115.5, 115.5, 59.5, 55.6, 40.7, 28.3.

General procedure for the preparation of products 3q–3x in Table 3

1-(*p*-Nitrophenyl)-3-methoxycarbonyl-1,2,3,4-tetrahydro-β-carboline (3q).[4a] The starting material of L-tryptophan methyl ester **1d** (91 mg, 0.5 mmol) and *p*-nitrobenzaldehyde **2a** (91 mg, 0.6 mmol) was dissolved in HFIP (0.8 mL) under nitrogen atmosphere. The resulting solution was refluxed and monitored by TLC. After completion, HFIP was removed by distillation. The residue was purified by column chromatography to afford the *cis*/*trans* diastereoisomeric mixture of **3q** (154 mg, 98%) as yellow solid.

*cis-**3q**.* Yield 51%; yellow solid; mp = 150–151 °C; (lit.[4a] mp = 152–153 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.21 (d, J = 8.4 Hz, 2H), 7.59 (d, J = 8.8 Hz, 2H), 7.56 (d, J = 7.2 Hz, 1H), 7.44 (br s, 1H), 7.22–7.24 (m, 1H), 7.12–7.19 (m, 2H), 5.38 (s, 1H), 3.98 (dd, J = 4.0, 11.2 Hz, 1H), 3.83 (s, 3H), 3.26 (ddd, J = 1.6, 4.0, 15.2 Hz, 1H), 2.99–3.06 (m, 1H), 2.61 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.9, 148.2, 148.0, 136.3, 132.9, 129.6, 126.8, 124.1, 122.4, 119.9, 118.4, 111.0, 109.5, 58.0, 56.5, 52.4, 25.4.

*trans-**3q**.* Yield: 47%; yellow solid; mp = 207–208 °C; (lit.[4a] mp = 205–207 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.17 (d, J = 8.8 Hz, 2H), 7.60 (br s, 1H), 7.57 (d, J = 7.6 Hz, 1H), 7.49 (d, J = 8.8 Hz, 2H), 7.27 (d, J = 7.6 Hz, 1H), 7.13–7.21 (m, 2H), 5.53 (s, 1H), 3.93 (t, J = 6.0 Hz, 1H), 3.72 (s, 3H), 3.28 (ddd, J = 1.2, 5.6, 15.6 Hz, 1H), 3.16 (ddd, J = 1.2, 6.4, 15.6 Hz, 1H), 2.65 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.9, 149.4, 147.3, 136.2, 131.6, 129.2, 126.6, 123.7, 122.3, 119.7, 118.3, 111.0, 108.7, 54.0, 52.3, 52.2, 24.6.

1-Phenyl-3-methoxycarbonyl-1,2,3,4-tetrahydro-β-carboline (3r).[4a]

*cis-**3r**.* Yield 51%; white solid; mp = 221–222 °C; (lit.[4a] mp = 223–224 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.53–7.55 (m, 1H), 7.44 (br s, 1H), 7.34–7.39 (m, 5H), 7.18–7.21 (m, 1H), 7.09–7.16 (m, 2H), 5.23 (s, 1H), 3.98 (dd, J = 3.6, 11.2 Hz, 1H), 3.81 (s, 3H), 3.23 (ddd, J = 2.0, 4.4, 15.2 Hz, 1H), 2.97–3.04 (m, 1H), 2.46 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.2, 140.5, 136.1, 134.5, 128.9, 128.6, 127.0, 121.9, 119.6, 118.2, 110.9, 108.8, 58.6, 56.8, 52.3, 25.6.

*trans-**3r**.* Yield 46%; white solid; mp = 176–177 °C; (lit.[4a] mp = 175–176 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.66 (br s, 1H), 7.54–7.56 (m, 1H), 7.28–7.34 (m, 3H), 7.23–7.26 (m, 2H), 7.19–7.22 (m, 1H), 7.10–7.17 (m, 2H), 5.37 (s, 1H), 3.95 (t, J = 5.6 Hz, 1H), 3.70 (s, 3H), 3.26 (dd, J = 5.2, 15.6 Hz, 1H), 3.12 (ddd, J = 1.6, 6.8, 15.6 Hz, 1H), 2.48 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.1, 141.9, 136.1, 133.2, 128.7, 128.4, 128.1, 126.9, 121.9, 119.5, 118.2, 110.9, 108.4, 54.9, 52.5, 52.1, 24.6.

1-(*p*-Bromophenyl)-3-methoxycarbonyl-1,2,3,4-tetrahydro-β-carboline (3s).[4a]

*cis-**3s**.* Yield 52%; white solid; mp = 164–165 °C; (lit.[4a] mp = 160–161 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 (d, J = 7.2 Hz, 1H), 7.49 (d, J = 8.0 Hz, 2H), 7.42 (br s, 1H), 7.26 (d, J = 7.6 Hz, 2H), 7.21 (d, J = 7.2 Hz, 1H), 7.10–7.17 (m, 2H), 5.21 (s, 1H), 3.95 (dd, J = 4.0, 10.8 Hz, 1H), 3.81 (s, 3H), 3.23 (ddd, J = 1.6, 4.0, 14.8 Hz, 1H), 2.96–3.03 (m, 1H), 2.47 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.0, 139.8, 136.1, 134.0, 132.1, 130.3, 127.0, 122.5, 122.1, 119.7, 118.3, 110.9, 109.1, 58.1, 56.7, 52.3, 25.6.

*trans-**3s**.* Yield 41%; white solid; mp = 174–175 °C; (lit.[4a] mp = 175–176 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56 (br s, 1H), 7.55 (d, J = 7.6 Hz, 1H), 7.45 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 7.6 Hz, 1H), 7.12–7.19 (m, 4H), 5.38 (s, 1H), 3.94 (t, J = 6.0 Hz, 1H), 3.72 (s, 3H), 3.26 (ddd, J = 0.8, 5.6, 15.6 Hz, 1H), 3.14 (ddd, J = 1.2, 6.8, 15.6 Hz, 1H), 2.54 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.1, 141.0, 136.1, 132.6, 131.8, 130.1, 126.9, 122.1, 122.1, 119.6, 118.3, 110.9, 108.5, 54.3, 52.5, 52.2, 24.5.

1-(2-Fluorophenyl)-3-methoxycarbonyl-1,2,3,4-tetrahydro-β-carboline (3t).[4j]

*cis-**3t**.* Yield 44%; white solid; mp = 163–164 °C; 1H NMR (400 MHz, CDCl3): δ 7.59 (br s, 1H), 7.52–7.54 (m, 1H), 7.29–7.38 (m, 2H), 7.21–7.24 (m, 1H), 7.09–7.16 (m, 4H), 5.67 (s, 1H), 3.98 (dd, J = 4.0, 11.2 Hz, 1H), 3.81 (s, 3H), 3.23 (ddd, J = 2.0, 4.0, 15.2 Hz, 1H), 2.96–3.04 (m, 1H), 2.51 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.1, 160.9 (d, J = 244.0 Hz), 136.0, 133.5, 133.0, 129.9 (d, J = 4.0 Hz), 127.6 (d, J = 13.0 Hz), 127.0, 124.8 (d, J = 3.0 Hz), 122.0, 119.6, 118.2, 115.7 (d, J = 21.0 Hz), 110.9, 109.1, 56.7, 52.3, 50.9 (d, J = 4.0 Hz), 25.5.

*trans-**3t**.* Yield 48%; white solid; mp = 197–198 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (br s, 1H), 7.55 (d, J = 7.2 Hz, 1H), 7.24–7.30 (m, 2H), 7.10–7.18 (m, 3H), 6.97–7.03 (m, 2H), 5.79 (s, 1H), 3.92 (dd, J = 5.2, 8.0 Hz, 1H), 3.73 (s, 3H), 3.25 (dd, J = 4.8, 15.2 Hz, 1H), 3.06 (ddd, J = 1.2, 8.0, 15.2 Hz 1H), 2.63 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.8, 160.7 (d, J = 244.0 Hz), 136.1, 131.8, 129.6 (d, J = 13.0 Hz), 129.6, 128.9 (d, J = 14.0 Hz), 126.8, 124.1 (d, J = 3.0 Hz), 122.1, 119.5, 118.2, 115.7 (d, J = 22.0 Hz), 110.9, 109.2, 52.3, 52.2, 48.1 (d, J = 4.0 Hz), 24.9.

1-(2-Hydroxyphenyl)-3-methoxycarbonyl-1,2,3,4-tetrahydro-β-carboline (3u).[4a,6d]

*cis-**3u**.* Yield 53%; light yellow solid; mp = 175–176 °C; (lit.[4a] mp = 162–164 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.15 (br s, 1H) 7.49–7.51 (m, 1H), 7.36 (br s, 1H), 7.24–7.28 (m, 2H), 7.17–7.19 (m, 1H), 7.06–7.14 (m, 2H), 6.90–6.94 (m, 1H), 6.82 (d, J = 8.0 Hz, 1H), 5.35 (s, 1H), 3.92 (dd, J = 4.0, 11.2 Hz, 1H), 3.86 (s, 3H), 3.42 (br s, 1H), 3.30 (ddd, J = 1.6, 4.4, 15.2 Hz, 1H), 3.03–3.10 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.9, 157.5, 136.3, 132.2, 130.1, 128.3, 127.0, 123.2, 122.1, 119.7, 119.4, 118.3, 117.8, 111.0, 107.7, 58.7, 56.4, 52.6, 24.7.

*trans-**3u**.* Yield 43%; white solid; mp = 164–165 °C; (lit.[6d] mp = 168–169 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.52 (br s, 1H) 7.51 (d, J = 7.2 Hz, 2H), 7.23 (d, J = 7.6 Hz, 2H), 7.11–7.17 (m, 3H), 6.84–6.89 (m, 2H), 5.59 (s, 1H), 4.13 (t, J = 4.8 Hz, 1H), 3.73 (s, 3H), 3.25–3.36 (m, 2H), 3.12 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.3, 157.3, 136.0, 131.3, 129.7, 128.4, 126.9, 124.0, 122.2, 119.6, 119.5, 118.3, 117.5, 111.0, 106.7, 53.9, 53.0, 52.3, 23.6.

1-(4-Methoxyphenyl)-3-methoxycarbonyl-1,2,3,4-tetrahydro-β-carboline (3v).[4a]

*cis-**3v**.* Yield 46%; white solid; mp = 125–126 °C; (lit.[4a] mp = 125–127 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52–7.54 (m, 1H), 7.46 (br s, 1H), 7.28 (d, J = 8.4 Hz, 2H), 7.19–7.22 (m, 1H), 7.09–7.16 (m, 2H), 6.89 (d, J = 8.8 Hz, 2H), 5.19 (s, 1H), 3.97 (dd, J = 4.0, 11.2 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.22 (ddd, J = 1.6, 4.0, 15.2 Hz, 1H), 2.96–3.03 (m, 1H), 2.41 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.2, 159.7, 136.0, 135.0, 132.7, 129.7, 127.1, 121.8, 119.5, 118.1, 114.2, 110.9, 108.8, 58.0, 56.9, 55.3, 52.2, 25.7.

*trans-**3v**.* Yield 41%; white solid; mp = 188–189 °C; (lit.[4a] mp = 189–190 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (br s, 1H), 7.55 (d, J = 6.8 Hz, 1H), 7.10–7.22 (m, 5H), 6.84 (d, J = 8.4 Hz, 2H), 5.34 (s, 1H), 3.95 (t, J = 6.0 Hz, 1H), 3.78 (s, 3H), 3.70 (s, 3H), 3.26 (dd, J = 5.2, 15.2 Hz, 1H), 3.11 (dd, J = 6.8, 15.2 Hz, 1H), 2.28 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.1, 159.3, 136.1, 134.0, 133.5, 129.5, 126.9, 121.8, 119.4, 118.2, 114.0, 110.9, 108.2, 55.3, 54.2, 52.4, 52.1, 24.6.

1-Pentyl-3-methoxycarbonyl-1,2,3,4-tetrahydro-β-carboline (3w).[4j]

*cis-**3w**.* Yield 50%; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.79 (br s, 1H), 7.48 (d, J = 7.6 Hz, 1H), δ 7.32 (d, J = 8.0 Hz, 1H), 7.16 (t, J = 7.2 Hz, 1H), 7.11 (t, J = 7.2 Hz, 1H), 4.17–4.22 (m, 1H), 3.83 (s, 3H), 3.79 (dd, J = 8.0, 11.2 Hz, 1H), 3.15 (ddd, J = 1.6, 4.0, 14.8 Hz, 1H), 2.78–2.85 (m, 1H), 2.08 (br s, 1H), 1.91–1.95 (m, 1H) 1.67–1.75 (m, 1H), 1.44–1.56 (m, 2H), 1.33–1.40 (m, 4H), 0.90 (t, J = 3.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.7, 135.9, 135.7, 127.2, 121.7, 119.6, 118.0, 110.8, 108.1, 56.5, 52.7, 52.2, 34.9, 32.1, 26.0, 25.0, 22.5, 14.1.

*trans-**3w**.* Yield 41%; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.76 (br s, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.08–7.17 (m, 2H), 4.21–4.24 (m, 1H), 3.98 (dd, J = 5.2, 7.2 Hz, 1H), 3.75 (s, 3H), 3.12 (ddd, J = 1.2, 5.2, 15.6 Hz, 1H), 2.99 (ddd, J = 1.2, 7.2, 15.2 Hz, 1H), 1.90 (br s, 1H), 1.70–1.82 (m, 2H), 1.44–1.58 (m, 2H), 1.28–1.40 (m, 4H), 0.91 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.3, 135.8, 135.7, 127.1, 121.6, 119.4, 118.0, 110.7, 106.9, 52.6, 52.1, 50.3, 35.7, 31.9 25.9, 25.0, 22.6, 14.1.

1-Isopropyl-3-methoxycarbonyl-1,2,3,4-tetrahydro-β-carboline (3x).[4j]

*cis-**3x**.* Yield 49%; light yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.83 (br s, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.16 (t, J = 6.8 Hz, 1H), 7.11 (t, J = 6.8 Hz, 1H), 4.15–4.18 (m, 1H), 3.82 (s, 3H), 3.75 (dd, J = 4.4, 11.6 Hz, 1H), 3.12 (ddd, J = 1.6, 4.0, 14.8 Hz, 1H), 2.75–2.82 (m, 1H), 2.18–2.25 (m, 1H), 1.99 (br s, 1H), 1.16 (d, J = 6.8 Hz, 3H), 0.88 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.8, 135.9, 135.0, 127.2, 121.6, 119.5, 117.9, 110.7, 109.2, 57.8, 56.3, 52.1, 31.7, 25.9, 19.0, 16.4.

*trans-**3x**.* Yield 41%; light yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.76 (br s, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.30 (d, J = 7.6 Hz, 1H), 7.08–7.17 (m, 2H), 4.12 (d, J = 4.8 Hz, 1H), 4.02 (t, J = 5.6 Hz, 1H), 3.70 (s, 3H), 3.01–3.13 (m, 2H), 2.01–2.11 (m, 2H), 1.11 (d, J = 6.8 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.6, 135.8, 134.6, 127.1, 121.5, 119.3, 118.0, 110.6, 107.9, 55.3, 53.5, 52.0, 32.9, 24.6 19.5, 17.8.

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11 More than 80% of HFIP could be recovered by distillation. The recovery and reuse experiment showed that the reaction time did not increase and the chemical yield did not decrease when use the recovered HFIP.

12 Because aldehydes are sensitive to air under refluxing conditions, all of the reactions were performed under nitrogen atmosphere.

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