One-pot three-component synthesis of highly substituted piperidines using 1-methyl-2-oxopyrrolidinium hydrogen sulfate

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1-Methyl-2-oxopyrrolidinium hydrogen sulfate ([Hpyro][HSO_4]) is used as an ionic liquid catalyst for the one-pot three-component synthesis of highly substituted piperidines from aromatic aldehydes, anilines and β–ketoesters in refluxing ethanol. This homogeneous catalyst procedure has the advantages of easy work-up, no need for column chromatography, simple and readily available precursors, and good to high yields.

Keywords: ionic liquid, [Hpyro][HSO_4], heterocycle, piperidine, homogeneous catalyst

In recent years, ionic liquids (ILs) have attracted considerable attention as reaction media and catalysts because of their unique properties such as a wide liquid range, non-flammability, non-volatile, thermal stability, low vapour pressure, and the ease of handling.[1–3]

Synthesis of six-membered nitrogen heterocyclic compounds such as piperidines and their analogues is very important because of their biological activities such as antimalarial,[4] antihypertensive,[5] antibacterial,[6] neuro-protective,[7,8] anticonvulsant and anti-inflammatory agents.[9,10] Furthermore, these compounds are intricately involved in the MAO based mechanism of Parkinson's disease[11,12] and as inhibitors of farnesyltransferase (Fig. 1),[13,14] and dihydroorate dehydrogenase.[15] In this respect, substituted piperidines have been identified as an important class of therapeutic agents in the treatment of influenza,[16–18] cancer metastasis,[19–21] viral infections including AIDS,[22,23] and diabetes.[24,25]

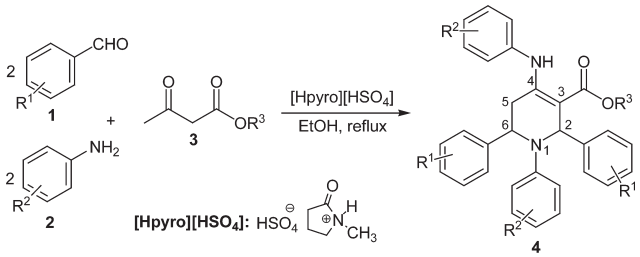
Recently, the synthesis of highly substituted piperidines have been reported using multi-component reactions in the presence of L-proline/TFA,[4] $InCl_3$,[26,27] bromodimethylsulfonium bromide (BDMS),[28] tetrabutylammonium tribromide (TBATB),[29] iodine,[30] cerium ammonium nitrate (CAN),[31] $ZrOCl_2{\cdot}8H_2O$,[32] $BF_3{\cdot}SiO_2$,[33] picric acid[34] and $Bi(NO_3)_3{\cdot}5H_2O$[35] as catalyst.

As part of our continuing interest in the development of multi-component reactions,[36–39] especially the synthesis of piperidines,[40,41] we report here an efficient and convenient procedure for the synthesis of highly substituted piperidines via a one-pot three-component reaction between aromatic aldehydes, anilines and β–ketoesters catalysed by 1-methyl-2-oxopyrrolidinium hydrogen sulfate [Hpyro][HSO_4] in refluxing ethanol (Scheme 1).

Results and discussion

Initially, 4-methylbenzaldehyde was reacted with aniline and ethyl acetoacetate in the presence of [Hpyro][HSO_4] (0.02 g, 10 mol%) in ethanol at ambient temperature for 20 h to give the corresponding highly substituted piperidines 73% yield. The reaction between 4-methylbenzaldehyde, aniline and ethyl acetoacetate was chosen as a model to study the optimum conditions. As shown in Table 1, the best result was obtained in the presence of 15 mol% of [Hpyro][HSO_4] in refluxing ethanol (Table 1, entry 9). Note that in the absence of [Hpyro][HSO_4], no conversion to the product was obtained even after 48 h. Also, when the reaction was carried out under solvent-free conditions, the product was obtained in a moderate yield (36%) that may be due to the lack of effective interaction of reactants with the catalyst.

Thus, several reactions between substituted benzaldehydes, anilines and methyl- and/or ethyl acetoacetate were examined, and the results are summarised in Table 2. As shown in Table 2, benzaldehydes with electron-deficient and/or electron-releasing group reacted efficiently with anilines to give the corresponding piperidines in good to high yields. The substituents on the benzene ring such as, OMe, Me, NO_2, F, Cl and Br were tolerated during the reaction. In all cases, the reaction afforded piperidine derivatives in good yields. All known products have been reported previously and were characterised by comparison of IR and NMR spectra with authentic samples. The relative stereochemistry of this class of compounds has



Scheme 1 Synthesis of highly functionalised piperidine **4**.

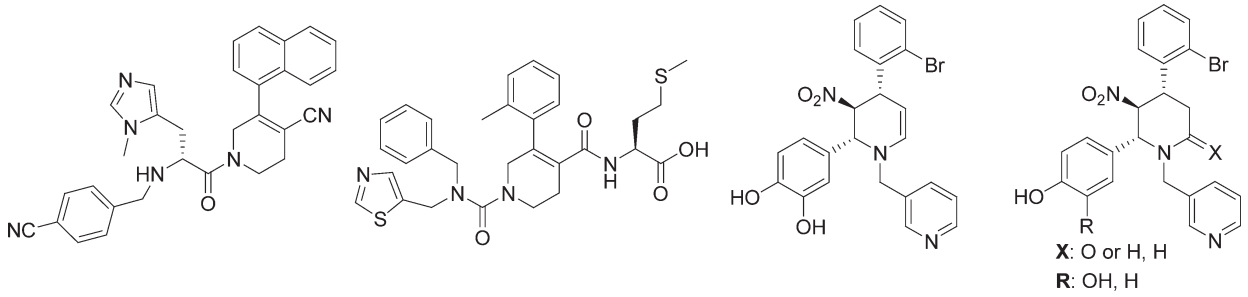


Fig. 1 Farnesyltransferase active compounds containing piperidine framework.[13,14]

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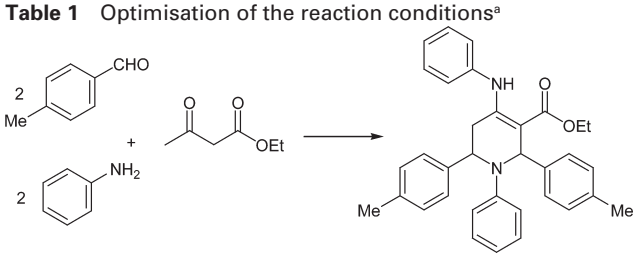
Table 1 Optimisation of the reaction conditions[a]



Entry	[Hpyro][HSO_4]/mol%	Solvent/temp.	Time/h	Yield/%[b]
1	10	EtOH/rt	20	73
2	15	EtOH/rt	16	78
3	20	EtOH/rt	16	77
4	25	EtOH/rt	16	78
5	15	MeOH/rt	16	78
6	15	CH_3CN/rt	18	51
7	15	H_2O/rt	24	trace
8	15	Neat/rt	24	36
9	15	EtOH/reflux	8	80
10	—	EtOH/tr	48	—

[a] Amount of materials in all reactions: 4-methyl benzaldehyde (2 mmol), aniline (2 mmol), and ethyl acetoacetate (1 mmol).
[b] Isolated yield.

been confirmed by X-ray crystallographic analysis,[26–35] and the stereochemistry of our products was confirmed by comparison of the spectroscopic data with those authentic samples (Table 3).

On the basis of the previous reports,[29–31,33,35,40] the proposed mechanism for the formation of piperidine **4** is illustrated in Scheme 2. First, the aromatic aldehyde **1** and *β*-ketoester **3** react with aniline **2** in the presence of [Hpyro][HSO_4] to give imine **A** and enamine **B**. Next, the reaction between imine **A** and enamine **B** leads to the intermediate **C** through an intermolecular Mannich-type reaction. The intermediate **C** reacts with aldehyde **1** to generate intermediate **D**. Then, tautomerisation of **D** generates intermediate **E**, which immediately undergoes intramolecular Mannich-type reaction to produce intermediate **F**. In the final step, tautomerisation of the intermediate **F** generates the desired piperidine **4** due to conjugation with the ester group.

To show the efficiency and the applicability of the present work for the synthesis of functionalised piperidines, we compared results of [Hpyro][HSO_4] with previously reported catalysts in the synthesis of compounds **4b**, **4e** and **4h** (Table 4). The results clearly show that [Hpyro][HSO_4] can act as an effective and efficient catalyst with respect to yields and reaction times.

In summary, the use of 1-methyl-2-oxopyrrolidinium hydrogen sulfate as an ionic liquid catalyst is reported for the synthesis of highly substituted piperidines via one-pot three-component reaction between aromatic aldehydes, anilines and *β*–ketoesters in refluxing ethanol in good to high yields. This methodology offered several advantages such as mild reaction conditions, simplicity in operation, no need for column chromatography and has a green aspect by using ethanol as solvent.

Experimental

Melting points were obtained on an Electrothermal 9100 apparatus. The ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 Avance instrument with $CDCl_3$ as solvent at 400 and 100 MHz, respectively. All reagents were purchased from Merck (Darmastadt, Germany), Acros (Geel, Belgium) or Fluka (Buchs, Switzerland), and used without further purification.

Preparation of 1-methyl-2-oxopyrrolidinium hydrogen sulfate [Hpyro][HSO_4]

Under vigorous stirring, 1-methylpyrrolidin-2-one was placed in flask and equal-molar sulfuric acid was added dropwise slowly at room temperature. Then the system was slowly heated up to 90 °C, stirred for 2 h after which the water was removed under vacuum at 90 °C to give [Hpyro][HSO_4] as a light yellow viscous liquid.[42]

Synthesis of highly substituted piperidine **4***; general procedure*

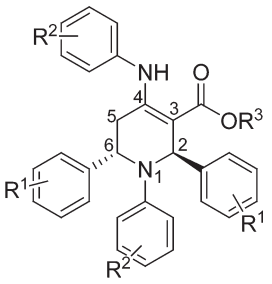
First, a solution of aromatic amine (2 mmol) and *β*-ketoester (1 mmol) in ethanol (5 mL) was stirred for 30 min in the presence of [Hpyro][HSO_4] (0.03 g, 15 mol%) at ambient temperature. Next, the aromatic aldehyde (2 mmol) was added and the reaction mixture stirred under refulx. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature. The resulting precipitates were collected by filtration and washed

Table 2 The synthesis of highly functionalised piperidine **4**

Entry	R^1	R^2	R^3	Product	Time/h	Yield/%[a]	M.p./ºC	Lit. m.p./°C[Ref. b]
1	4-Me	H	Et	**4a**	8	80	228–230	228–231[30]
2	4-Me	H	Me	**4b**	8	79	214–217	215–217[30]
3	4-F	H	Me	**4c**	8	81	202–204	205[4]
4	4-Cl	H	Me	**4d**	9	80	185–186	189–191[28]
5	3-Cl	H	Me	**4e**	10	78	218–220	220[4]
6	4-OMe	H	Me	**4f**	12	67	178–181	180[4]
7	3-NO_2	H	Me	**4g**	14	33	180–181	182–183[30]
8	H	H	Me	**4h**	8	77	190–192	194[4]
9	3-Cl	4-Cl	Et	**4i**	10	82	187–188	190[4]
10	4-Cl	4-Me	Me	**4j**	9	79	213–215	213–213[32]
11	4-OMe	4-Cl	Me	**4k**	12	71	193–195	195[4]
12	4-Me	4-Br	Me	**4l**	8	73	228–231	230–232[30]
13	4-F	4-Cl	Me	**4m**	9	80	173–175	176[4]
14	4-Me	4-Me	Me	**4n**	8	75	204–205	206–208[30]
15	4-F	H	Et	**4o**	10	73	200–202	204–208[35]
16	4-Cl	4-Me	Et	**4p**	12	74	225–228	227–229[35]
17	4-Me	3,4-di-Cl	Et	**4q**	11	74	173–175	173–175[40]
18	H	4-Me	Et	**4r**	10	80	199–202	196–198[35]
19	H	4-Cl	Et	**4s**	8	77	197–198	201–202[31]
20	4-F	4-Me	Me	**4t**	8	73	200–202	200–202[40]
21	4-Me	4-F	Et	**4u**	9	78	183–185	183–185[40]
22	3-Me	H	Et	**4v**	8	74	154–156	149–151[41]
23	3-Br	H	Et	**4w**	8	77	165–167	164–167[41]

[a] Isolated yield.
[b] References refer to known products as mentioned in the literature.

Table 3 Comparison of our spectroscopic data of some products with authentic samples



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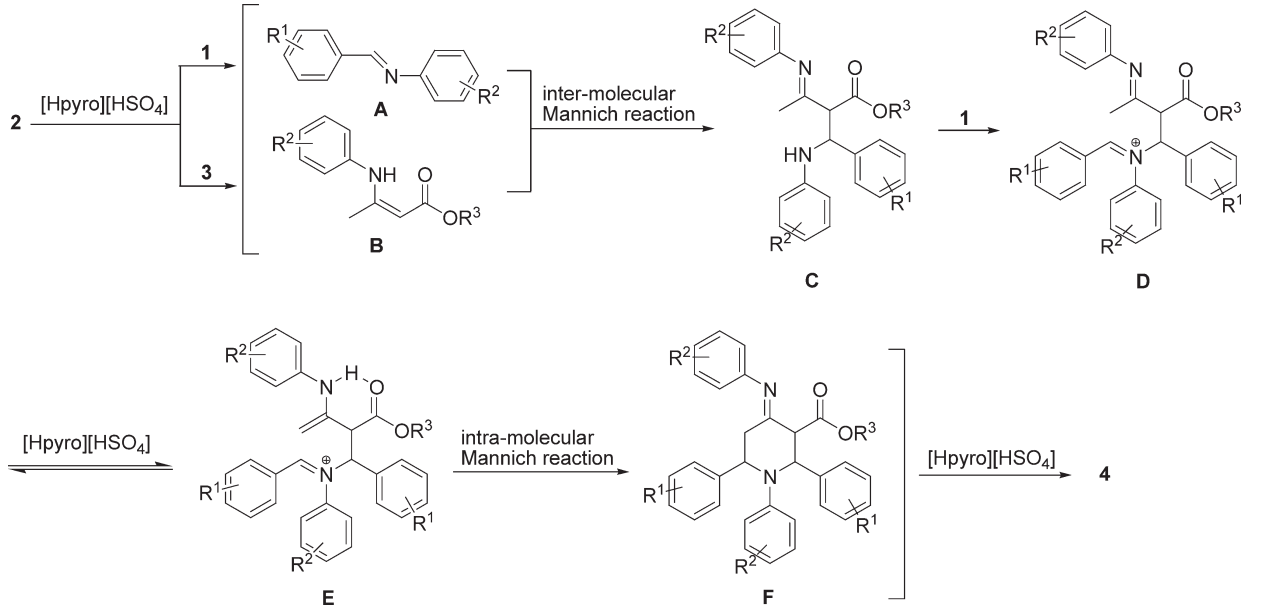
Entry	Compound	H shift (found)	H shift (lit.)	Ref.[a]
1	**4a**	H-2: 6.45 (s) H′, H″-5: 2.80 (dd, *J* = 15.2, 2.4 Hz), 2.90 (dd, *J* = 15.2, 5.6 Hz) H-6: 5.15 (d, *J* = 2.6 Hz)	H-2: 6.40 (s) H′, H″-5: 2.76 (dd, *J* = 15.2, 2.4 Hz), 2.86 (dd, *J* = 15.2, 5.6 Hz) H-6: 5.11 (d *J* = 2.4 Hz)	30
2	**4b**	H-2: 6.42 (s) H′, H″-5: 2.72 (dd, *J* = 15.2, 2.4 Hz), 2.84 (dd, *J* = 15.2, 5.6 Hz) H-6: 5.12 (d, *J* = 2.9 Hz)	H-2: 6.37 (s) H′, H″-5: 2.74 (dd, J = 15.2, 2.4 Hz), 2.84 (dd, *J* = 15.2, 5.6 Hz) H-6: 5.08–5.09 (m)	28
3	**4d**	H-2: 6.40 (s) H′, H″-5: 2.74 (dd, *J* = 15.2, 2.4 Hz), 2.86 (dd, *J* = 15.2, 5.6 Hz) H-6: 5.09 (br s)	H-2: 6.35 (s) H′, H″-5: 2.74 (dd, *J* = 15.2, 2.4 Hz), 2.82 (dd, *J* = 15.2, 5.6 Hz) H-6: 5.09–5.10 (m)	28
4	**4h**	H-2: 6.42 (s) H′, H″-5: 2.73 (dd, *J* = 15.1, 2.6 Hz), 2.84 (dd, *J* = 15.1, 5.4 Hz) H-6: 5.11 (d, *J* = 3.5 Hz)	H-2: 6.46 (s) H′, H″-5: 2.77 (dd, *J* = 15.3, 2.3 Hz), 2.88 (dd, *J* = 15.3, 5.8 Hz) H-6: 5.15 (m)	26
5	**4l**	H-2: 6.35 (s) H′, H″-5: 2.74 (d, *J* = 15.2 Hz), 2.88 (dd, *J* = 15.2, 5.6 Hz) H-6: 5.10 (d, *J* = 3.6 Hz)	H-2: 6.31 (s) H′, H″-5: 2.70 (dd, *J* = 15.2, 2.4 Hz), 2.84 (dd, *J* = 15.2, 5.6 Hz) H-6: 5.06 (d, *J* = 3.6 Hz)	30
6	**4n**	H-2: 6.39 (s) H′, H″-5: 2.76 (dd, *J* = 15.1, 2.4 Hz), 2.87 (dd, *J* = 15.2, 5.6 Hz) H-6: 5.11 (d, *J* = 3.2 Hz)	H-2: 6.35 (s) H′, H″-5: 2.72 (dd, *J* = 15.2, 2.4 Hz), 2.82 (dd, *J* = 15.2, 5.6 Hz) H-6: 5.07 (d, *J* = 4.0 Hz)	30
7	**4p**	H-2: 6.37 (s) H′, H″-5: 2.74 (dd, *J* = 15.2, 2.4 Hz), 2.86 (dd, *J* = 15.2, 5.6 Hz) H-6: 5.10 (d, *J* = 2.8 Hz)	H-2: 6.29 (-) H′, H″-5: 2.70 (dd, *J* = 15.2, 2.4 Hz), 2.77 (dd, *J* = 15.2, 5.2 Hz) H-6: 5.05 (br s)	35
8	**4r**	H-2: 6.47 (s) H′, H″-5: 2.78 (dd, *J* = 15.0, 2.0 Hz), 2.88 (dd, *J* = 15.0, 5.6 Hz) H-6: 5.16 (d, *J* = 3.6 Hz)	H-2: 6.43 (-) H′, H″-5: 2.72 (dd, *J* = 15.2, 2.0 Hz), 2.82 (dd, *J* = 15.2, 5.6 Hz) H-6: 5.11 (d, *J* = 3.4 Hz)	35

[a] In these references the structure as well as the relative stereochemistry of this class of heterocycles have been confirmed by single X-ray crystallographic analysis.



Scheme 2 Proposed reaction mechanism for synthesis of highly functionalised piperidines **4**.

Table 4 Comparation of [Hpyro][HSO_4] with reported catalysts for the synthesis of highly substituted piperidine derivatives

Entry	Compound	Catalyst /Conditions	Time /h	Yield /%	Ref.
1	**4b**	$InCl_3/CH_3CN$, r.t.	24	50	26
		$BDMS/CH_3CN$, r.t.	3	80	28
		TBATB/EtOH, r.t.	8	78	29
		I_2/MeOH, r.t.	8	84	30
		CAN/CH_3CN, r.t.	22	85	31
		$ZrOCl_2{\cdot}8H_2O$/EtOH, reflux	—	—	32
		p-TsOH·H_2O/EtOH, r.t.	7	89	40
		$BF_3{\cdot}SiO_2$/MeOH, 65 °C	—	—	33
		$Bi(NO_3)_3{\cdot}5H_2O$/EtOH, r.t.	18	73	35
		L-proline/TFA/CH_3CN, 20–30 °C	—	—	4
		[Hpyro][HSO_4]/EtOH, reflux	8	79	—[a]
2	**4d**	$InCl_3/CH_3CN$, r.t.	—	—	26
		$BDMS/CH_3CN$, r.t.	3	76	28
		TBATB/EtOH, r.t.	10	82	29
		I_2/MeOH, 55 °C	6	85	30
		CAN/CH_3CN, r.t.	15	86	31
		$ZrOCl_2{\cdot}8H_2O$/EtOH, reflux	4	80	32
		p-TsOH·H_2O/EtOH, r.t.	7	86	40
		$BF_3{\cdot}SiO_2$/MeOH, 65 °C	—	—	33
		$Bi(NO_3)_3{\cdot}5H_2O$/EtOH, r.t.	18	76	35
		L-proline/TFA/CH_3CN, 20–30 °C	17	70	4
		[Hpyro][HSO_4]/EtOH, reflux	9	80	—[a]
3	**4h**	$InCl_3/CH_3CN$, r.t.	24	60	26
		$BDMS/CH_3CN$, r.t.	3	75	28
		TBATB/EtOH, r.t.	24	74	29
		I_2/MeOH, r.t.	8	81	30
		CAN/CH_3CN, r.t.	20	82	31
		$ZrOCl_2{\cdot}8H_2O$/EtOH, reflux	3.5	80	32
		p-TsOH·H_2O/EtOH, r.t.	10	78	40
		$BF_3{\cdot}SiO_2$/MeOH, 65 °C	9	78	33
		$Bi(NO_3)_3{\cdot}5H_2O$/EtOH, r.t.	12	81	35
		L-proline/TFA/CH_3CN, 20–30 °C	17	70	4
		[Hpyro][HSO_4]/EtOH, reflux	8	77	—[a]

[a] This work.

with EtOH (3 × 2 mL) to give the pure product. Spectral data of selected products are represented below.

Ethyl-(2RS, 6SR)-1-phenyl-4-(phenylamino)-2,6-di(4-methyphenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (**4a**): White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.50 (3H, t, *J* = 7.0 Hz, $OCH_2C\underline{H}_3$), 2.36 (3H, s, CH_3), 2.37 (3H, s, CH_3), 2.80 (1H, dd, *J* = 15.2, 2.4 Hz, H′-5), 2.90 (1H, dd, *J* = 15.2, 5.6 Hz, H″-5), 4.33–4.38 (1H, m, OCH_aH_b), 4.47–4.51 (1H, m, OCH_aH_b), 5.15 (1H, d, *J* = 3.2 Hz, H-6), 6.33 (2H, d, *J* = 7.6 Hz, ArH), 6.45 (1H, s, H-2), 6.57 (2H, d, *J* = 8.8 Hz, ArH), 6.63 (1H, t, *J* = 7.0 Hz, ArH), 7.06–7.31 (13H, m, ArH), 10.33 (1H, s, NH).

Methyl-(2RS, 6SR)-1-phenyl-4-(phenylamino)-2,6-di(4-methyphenyl)-1,2,5,6-tetrahydro-pyridine-3-carboxylate (**4b**): White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.25 (3H, s, CH_3), 2.32 (3H, s, CH_3), 2.72 (1H, dd, *J* = 15.2, 2.4 Hz, H'-5), 2.84 (1H, dd, *J* = 15.2, 5.6 Hz, H″-5), 3.93 (3H, s, OCH_3), 5.12 (1H, d, *J* = 2.9 Hz, H-6), 6.30 (2H, d, *J* = 8.0 Hz, ArH), 6.42 (1H, s, H-2), 6.48 (2H, d, *J* = 8.8 Hz, ArH), 6.60 (1H, t, *J* = 7.2 Hz, ArH), 6.99–7.12 (11H, m, ArH), 7.20 (2H, d, *J* = 8.0 Hz, ArH), 10.27 (1H, s, NH).

Methyl-(2RS, 6SR)-2,6-bis(4-chlorophenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**4d**): White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.74 (1H, dd, *J* = 15.2, 2.4 Hz, H'-5), 2.86 (1H, dd, *J* = 15.2, 5.6 Hz, H″-5), 3.94 (3H, s, OMe), 5.09 (1H, br s, H-6), 6.39 (2H, d, *J* = 7.5 Hz, ArH), 6.40(1H, s, H-2), 6.56 (2H, d, *J* = 8.0 Hz, ArH), 6.64(1H, t, *J* = 7.0 Hz, ArH), 7.05–7.27 (13H, m, ArH), 10.26 (1H, s, NH).

Methyl-(2RS, 6SR)-1,2,6-triphenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**4h**): Light yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.73 (1H, dd, *J* = 15.1, 2.6 Hz, H'-5), 2.84 (1H, dd, *J* = 15.1, 5.4 Hz, H″-5), 3.98 (3H, s, OCH_3), 5.11 (1H, d, *J* = 3.5 Hz, H-6), 6.34 (2H, d, *J* = 7.2 Hz, ArH), 6.42(1H, s, H-2), 6.53 (2H, d, *J* = 7.2 Hz, ArH), 6.63 (1H, t, *J* = 7.0 Hz, ArH), 7.05–7.28 (15H, m, ArH), 10.29 (1H, s, NH).

Methyl-(2RS, 6SR)-4-(4-bromophenylamino)-1-(4-bromophenyl)-2,6-di(4-methyphenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (**4l**): White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.36 (3H, s, CH_3), 2.38 (3H, s, CH_3), 2.74 (1H, d, *J* = 15.2 Hz, H′-5), 2.88 (1H, dd, *J* = 15.2, 5.6 Hz, H″-5), 3.97 (3H, s, O CH_3), 5.10 (1H, d, *J* = 3.6 Hz H-6), 6.17 (2H, d, *J* = 8.4 Hz, ArH), 6.35 (1H, s, H-2), 6.42 (2H, d, *J* = 9.2 Hz, ArH), 7.05–7.25 (12H, m, ArH), 10.23 (1H, s, NH).

Methyl-(2RS, 6SR)-4-(4-methyphenylamino)-1,2,6-tri(4-methyphenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (**4n**): Light yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): 2.19 (3H, s, CH_3), 2.30 (3H, s, CH_3), 2.35 (3H, s, CH_3), 2.37 (3H, s, CH_3), 2.76 (1H, dd, *J* = 15.1, 2.4 Hz, H′-5), 2.87 (1H, dd, *J* = 15.2, 5.6 Hz, H″-5), 3.94 (3H, s, OCH_3), 5.11 (1H, d, *J* = 3.2 Hz, H-6), 6.21 (2H, d, *J* = 8.4 Hz, ArH), 6.39 (1H, s, H-2), 6.47 (2H, d, *J* = 8.8 Hz, ArH), 6.89–7.25 (12H, m, ArH), 10.21 (1H, s, NH).

Ethyl-(2RS, 6SR)-2,6-bis(4-chlorophenyl)-1-(4-methylphenyl)-4-(4-methylphenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**4p**): White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.46 (3H, t, *J* = 7.0 Hz, $OCH_2C\underline{H}_3$), 2.19 (3H, s, CH_3), 2.28 (3H, s, CH_3), 2.74 (1H, dd, *J* = 15.2, 2.4 Hz, H′-5), 2.86 (1H, dd, *J* = 15.2, 5.6 Hz, H″-5), 4.30–4.36 (1H, m, OCH_aH_b), 4.39–4.45 (1H, m, OCH_aH_b), 5.10 (1H, d, *J* = 2.8 Hz, H-6), 6.29 (2H, d, *J* = 8.0 Hz, ArH), 6.37 (1H, s, H-2), 6.46 (2H, d, *J* = 8.8 Hz,ArH), 6.97 (2H, d, *J* = 8.4 Hz,ArH), 7.05–7.27 (10H, m, ArH), 10.20 (1H, br s, NH).

Ethyl-(2RS, 6SR)-4-(3,4-dichlorophenylamino)-1-(3,4-dichlorophenyl)-2,6-di(4-methyphenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (**4q**): White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.50 (3H, t, *J* = 6.4 Hz, $OCH_2C\underline{H}_3$), 2.34 (3H, s, CH_3), 2.35 (3H, s, CH_3), 2.73 (1H, d, *J* = 15.2 Hz, H′-5), 2.90 (1H, dd, *J* = 15.2, 5.6 Hz, H″-5), 4.31–4.40 (1H, m, OCH_aH_b), 4.46–4.54 (1H, m, OCH_aH_b), 5.08 (1H, br s, H-6), 6.15 (2H, d, *J* = 7.2 Hz, ArH), 6.36 (1H, s, H-2), 6.42 (2H, d, *J* = 7.6 Hz, ArH), 6.95–7.25 (10H, m, ArH), 10.24 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 14.8 ($OCH_2\underline{C}H_3$), 21.6 (CH_3), 21.8 (CH_3), 33.4 (C-5), 55.3 (C-2), 58.3 (C-6), 59.8 ($O\underline{C}H_2CH_3$), 98.9 (C-3), 108.3, 114.6, 119.1, 123.5, 123.5, 126.9, 127.2, 127.4, 127.4, 128.2, 128.2, 128.7, 131.5, 131.9, 137.0, 138.0, 138.4, 142.2, 143.3, 146.0, 155.3 (C-4), 168.1 (C=O).

Ethyl-(2RS,6SR)-4-(4-methylphenylamino)-2,6-diphenyl-1-(4-methylphenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (**4r**): White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.50 (3H, t, *J* = 7.0 Hz, $OCH_2C\underline{H}_3$), 2.20 (3H, s, CH_3), 2.30 (3H, s, CH_3), 2.78 (1H, dd, *J* = 15.0, 2.0 Hz, H′-5), 2.88 (1H, dd, *J* = 15.0, 5.6 Hz, H″-5), 4.37 (1H, dq, *J* = 10.4, 7.0 Hz, OCH_aH_b), 4.49 (1H, dq, *J* = 10.4, 7.0 Hz, OCH_aH_b), 5.16 (1H, d, *J* = 3.6 Hz, H-6), 6.20 (2H, d, *J* = 8.0 Hz, ArH), 6.47 (1H, s, H-2), 6.48 (2H, d, *J* = 8.4 Hz, ArH), 6.92 (2H, d, *J* = 8.4 Hz, ArH), 6.93 (2H, d, *J* = 8.0, Hz), 7.21–7.39 (10H, m, ArH), 10.26 (1H, s, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ_c 14.9 ($OCH_2\underline{C}H_3$), 20.2 (CH_3), 20.9 (CH_3), 33.6 (C-5), 55.2 (C-2), 58.3 (C-6), 59.6 ($O\underline{C}H_2CH_3$), 97.8 (C-3), 112.9, 125.1, 125.9, 126.2, 126.5, 127.1, 127.2, 128.2, 128.6, 129.4, 129.5, 135.3, 135.5, 143.1, 144.4, 144.9, 156.4, (C-4), 168.3 (C=O).

Methyl-(2RS, 6SR)-4-(4-methylphenylamino)-2,6-bis(4-fluorophenyl)-1-(4-methylphenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (**4t**): White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.20 (3H, s, CH_3), 2.31 (3H, s, CH_3), 2.75 (1H, dd, *J* = 15.1, 2.4 Hz, H′-5), 2.83 (1H, dd, *J* = 15.1, 5.6 Hz, H″-5), 3.95 (3H, s, OCH_3), 5.11 (1H, br s, H-6), 6.31 (2H, d, *J* = 8.4 Hz, ArH), 6.37 (1H, s, H-2), 6.42 (2H, d, *J* = 8.8 Hz, ArH), 6.92 (2H, d, *J* = 8.4 Hz, ArH), 6.97–7.02 (6H, m, ArH), 7.12–7.15 (2H, m, ArH), 7.27–7.31 (2H, m, ArH), 10.22 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 20.1 (CH_3), 20.9 (CH_3), 33.7 (C-5), 51.0 (OCH_3), 54.7 (C-2), 57.3 (C-6), 97.2 (C-3), 113.0, 114.9 (d, *J* = 21.0 Hz), 115.4 (d, *J* = 21.0 Hz), 125.6, 125.8, 127.9 (d, *J* = 8.0 Hz), 128.2 (d, *J* = 7.0 Hz), 129.6, 135.0, 135.9, 138.4, 139.7, 144.5, 156.4 (C-4), 161.5 (d, $^1J_{CF}$ = 243.0 Hz), 161.9 (d, $^1J_{CF}$ = 244.0 Hz), 168.4 (C=O).

Ethyl-(2RS, 6SR)-4-(4-fluorophenylamino)-1-(4-fluorophenyl)-2,6-di-4-methylphenyl-1,2,5,6-tetrahydropyridine-3-carboxylate (**4u**): White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.49 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$), 2.36 (3H, s, CH_3), 2.39 (3H, s, CH_3), 2.67 (1H, dd, *J* = 15.2, 2.4 Hz, H′-5), 2.86 (1H, dd, *J* = 15.2, 5.8 Hz, H″-5), 4.36 (1H, dq, *J* = 10.5, 7.2 Hz, OCH_aH_b), 4.49 (1H, dq, *J* = 10.5, 6.8 Hz, OCH_aH_b), 5.08 (1H, d, *J* = 3.6 Hz, H-6), 6.25–6.29 (2H, m, ArH), 6.35 (1H, s, H-2), 6.44–6.48 (2H, m, ArH), 6.77–6.84 (4H, m, ArH), 7.06–7.23 (8H, m, ArH), 10.22 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 14.8 ($OCH_2\underline{C}H_3$), 21.0 (CH_3), 21.1 (CH_3), 33.6 (C-5), 55.4 (C-2), 58.1 (C-6), 59.7 ($O\underline{C}H_2CH_3$), 98.3 (C-3), 113.6 (d, *J* = 7.0 Hz), 115.2

(d, J = 22.0 Hz), 115.6 (d, J = 23.0 Hz), 126.9 (d, J = 23.0 Hz), 127.9 (d, J = 9.0 Hz), 129.0, 129.4, 134.0 (d, J = 3.0 Hz), 135.9, 136.9, 139.7, 140.7, 143.6, 155.0 (d, $^1J_{CF}$ = 234.0 Hz), 156.0 (C-4), 160.7 (d, $^1J_{CF}$ = 245.0 Hz), 168.2 (C=O).

Ethyl-(2RS, 6SR)-2,6-bis(3-methylphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**4v**): White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.51 (3H, t, J = 7.2 Hz, $OCH_2C\underline{H}_3$), 2.33 (3H, s, CH_3), 2.36 (3H, s, CH_3), 2.78 (1H, dd, J = 15.2, 2.0 Hz, H′-5), 2.91 (1H, dd, J= 15.2, 6.0 Hz, H″-5), 4.36 (1H, dq, J = 10.8, 7.2 Hz, OCH_aH_b), 4.51 (1H, dq, J = 10.8, 7.2 Hz, OCH_aH_b), 5.13 (1H, d, J = 4.0 Hz, H-6), 6.30 (2H, d, J = 7.6 Hz, ArH), 6.45 (1H, s, H-2), 6.56 (2H, d, J = 8.0 Hz, ArH), 6.64 (2H, d, J = 7.2 Hz, ArH), 6.98–7.22 (13H, m, ArH), 10.30 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 14.8 ($OCH_2\underline{C}H_3$), 21.5 (CH_3), 21.8 (CH_3), 33.6 (C-5), 55.2 (C-2), 58.2 (C-6), 59.5 ($O\underline{C}H_2CH_3$), 98.1 (C-3), 112.9, 115.9, 123.6, 123.6, 125.7, 126.0, 126.9, 127.0, 127.3, 127.8, 128.0, 128.5, 128.7, 128.8, 137.8, 137.9, 138.0, 142.7, 144.1, 147.1, 156.2 (C-4), 168.2 (C=O).

Ethyl-(2RS, 6SR)-2,6-bis(3-bromophenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**4w**): White solid; ^{1}HNMR (400 MHz, $CDCl_3$) δ_H 1.52 (3H, t, J =7.2 Hz, $OCH_2C\underline{H}_3$), 2.79 (1H, d, J = 15.0 Hz, H′-5), 2.89 (1H, dd, J = 15.2, 5.2 Hz, H″-5), 4.37 (1H, dq, J = 10.8, 7.2 Hz, OCH_aH_b), 4.54 (1H, dq, J = 10.8, 7.0 Hz, OCH_aH_b), 5.15 (1H, br, H-6), 6.41 (2H, d, J = 8.0 Hz, ArH), 6.42 (1H, s, H-2), 6.51 (2H, d, J = 8.0 Hz, ArH), 6.70 (1H, t, J = 7.2 Hz, ArH), 7.10–7.25 (9H, m, ArH), 7.30 (1H, s, ArH), 7.39 (1H, d, J =7.6 Hz, ArH), 7.44 (1H, d, J =7.6 Hz, ArH), 7.60 (1H, s, ArH), 10.34 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 14.9 ($OCH_2\underline{C}H_3$), 33.6 (C-5), 55.0 (C-2), 57.5 (C-6), 59.9 ($O\underline{C}H_2CH_3$), 97.3 (C-3), 113.0, 116.9, 122.7, 123.9, 125.1, 125.2, 126.1, 126.2, 129.1, 129.1, 129.4, 129.6, 129.7, 129.8, 130.3, 130.4, 137.6, 145.0, 146.3, 146.6, 155.8 (C-4), 167.9(C=O).

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