A Rapid Access to (±)-Sedamine and Some Original *N*-Benzyl Unsaturated Analogues

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Abstract: Reduction of *N*-alkyl-2-(2-hydroxy-2-phenylethyl)pyridinium salts using excess of sodium triacetoxyborohydride afforded exclusively the corresponding tetrahydropyridine derivative bearing a piperidine ring with a double bond in the 3,4-position. Furthermore, under these conditions, *syn*-1,3-amino alcohols were obtained in good yield and diastereoselectivity.

Key words: hydrides, diastereoselectivity, piperidines, pyridinium, reduction

A large number of alkaloids containing a piperidine ring are of plant or marine origin. Sedamine **1** (Figure 1) is one of the major components found in *Sedum acre L.*[1] in addition to around twenty mono- or disubstituted piperidinic compounds including norsedamine **2**. Its biosynthesis has been studied and is consistent with Robinson's classical biogenetic hypothesis starting from lysine.[2] The diastereoisomer of sedamine, allosedamine **3**, was first isolated from *Lobelia inflata*,[3] also known as Indian tobacco. This plant contains another known piperidinic alkaloid, lobeline **4**. Lobeline has been identified as a potential agonist/antagonist of the nicotinic acetyl choline receptors (nAChRs).[4] As a result, simplified lobeline analogues, such as sedamine or allosedamine and their unsaturated derivatives, have also been tested as potential nicotinic ligands[5] or acetyl choline esterase inhibitors.[6] Moreover, the piperidine nucleus has emerged as a crucial scaffold in a wide range of compounds with various pharmacological properties such that, a few years ago, it was pointed out that in one decade, between July 1988 through December 1998, over 12,000 piperidine derivatives had been involved in clinical or preclinical studies.[7]

In this context, it is not surprising that numerous asymmetric syntheses of sedamine **1** or allosedamine **3** have been published in the literature and some of them have been discussed in recent reviews.[8] These syntheses can be divided into two defined strategies: the first consists of introducing the side chain onto preformed pyridine or piperidine precursors, while the second involves constructing the piperidine core following an original and stereospecific multistep sequence. In previous work, our group has published the enantiospecific and stereoselective synthesis of sedamine[9] and allosedamine[10] in fourteen and eleven steps, respectively.

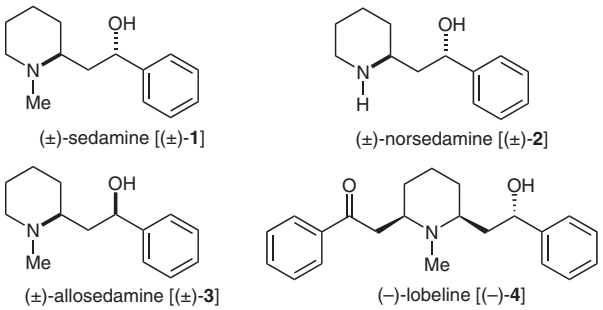

Figure 1 Structures of (±)-sedamine [(±)-**1**], (±)-norsedamine [(±)-**2**], (±)-allosedamine[(±)-**3**], (–)-lobeline [(–)-**4**]

However, in order to access one of these diastereoisomers in a rapid manner, we recently revisited a pyridine strategy published in the 1950s by Beyerman and co-workers.[11] By addition of a 2-picoline anion to benzaldehyde, the authors introduced the phenylethanol side chain into the pyridine moiety to obtain compound **5**, which, after quaternarization with methyl iodide,[11a] was hydrogenated in the presence of Adams' catalyst (PtO_2) (see Scheme 1). They finally obtained a mixture of racemic sedamine (±)-**1** and allosedamine (±)-**3** in modest yield.[11b]

In the 1990s, Terry and co-workers[6] described the hydride reduction of the same pyridinium derivative **6a**, with sodium borohydride in ethanol (Scheme 2). Under these conditions, a racemic mixture of 1,2,3,6-tetrahydropyridine derivatives (±)-**7a** and (±)-**8a**, which can be considered as unsaturated analogues of sedamine **2** and allosedamine **3**, were prepared and evaluated on nicotinic- and muscarinic-cholinergic receptors in the context of central nervous system diseases. It should be pointed out that yield and diastereoselectivity were not mentioned in this work. In the absence of experimental procedures and characterization data for these key intermediates, it was difficult for us to reproduce this reduction step (*vide infra*). Moreover, no explanation was provided by the authors to justify the position of the double bond in the piperidine ring.

Although there are various synthetic methods for the preparation of piperidines,[12] efficient, reliable, and convenient routes to substituted-1,2,5,6-tetrahydropyridines are still required. This latter class of compounds could serve as attractive starting materials for potential biologically active,

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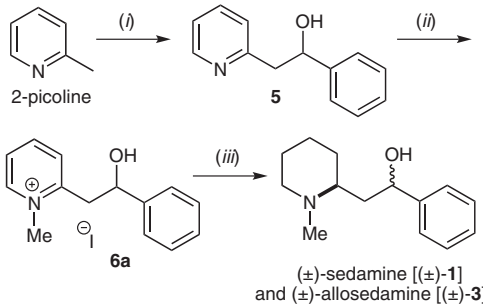
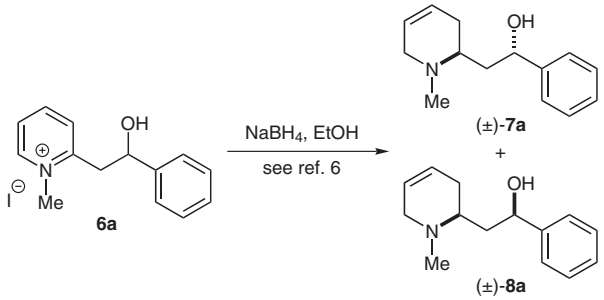


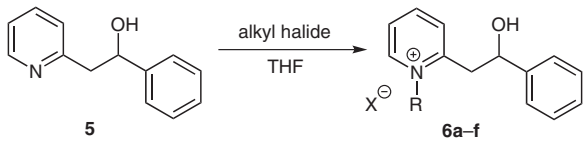
Scheme 1 *Reagents and conditions*: (i) *n*-BuLi, Et_2O, –70 °C then PhCHO, –70 °C to r.t., 38%; (ii) MeI, EtOH, nearly quantitative; (iii) H_2 (50 atm), PtO_2, MeOH, 24% [(±)-**1**)], 23% [(±)-**3**].



Scheme 2

highly substituted piperidine derivatives after chemical modification of the double bond.[13] Due to our continuing interest in this area and based on Terry's previous work, we decided to evaluate this methodology for the preparation of original sedamine and allosedamine analogues. Starting from the common 1-phenyl-2-(2-pyridyl)ethanol intermediate **5**, quaternarization in tetrahydrofuran with methyl iodide or selected benzyl bromides or chlorides afforded the corresponding insoluble pyridinium derivatives **6a–f**, which could easily be purified from the reaction mixture by simple filtration in 60–95% yields (Table 1).

Table 1 Quaternarization of Pyridine Derivative **5** with Various Alkyl Halides



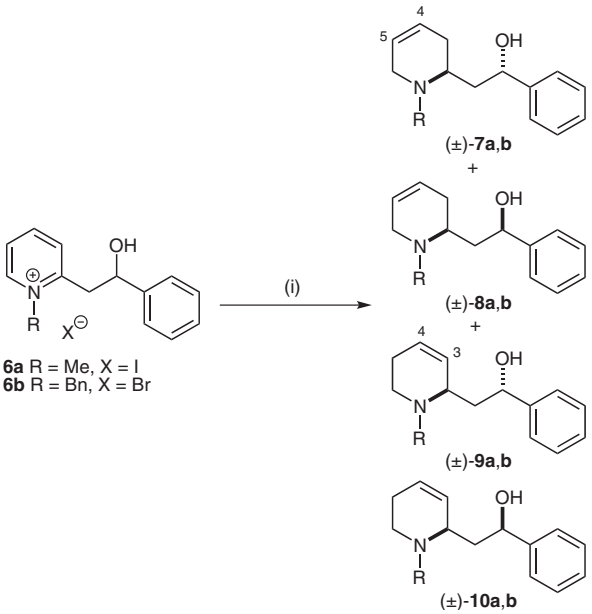
Entry	Alkyl halide[a]	Temp (°C)	Time (d)	Product	Yield (%)
1	MeI	37	2	**6a**	95
2	BnBr	37	3	**6b**	89
3	4-$BrC_6H_4CH_2Br$	37	3	**6c**	95
4	4-$O_2NC_6H_4CH_2Br$	r.t.	4	**6d**	65
5	4-$FC_6H_4CH_2Br$	r.t.	4	**6e**	60
6	4-$MeOC_6H_4CH_2Cl$	r.t.	7	**6f**	95[b]

[a] With benzyl halides, around 10% of KI was added.
[b] Compound **6f** was obtained as a brown oil.

As briefly described by Terry and co-workers,[6] the reduction of the methylpyridinium derivative **6a** was carried out in ethanol with sodium borohydride. Despite exhaustive screening of these reduction reaction conditions by varying different parameters, we were unable to isolate cleanly the two diastereoisomers (±)-**7a** and (±)-**8a** (Scheme 3).

In our hands (see Supporting Information for ^1H NMR analysis), a mixture of four tetrahydropyridine isomers (±)-**7a**/(±)-**8a** and (±)-**9a**/(±)-**10a** was obtained in 85% overall yield with a relative ratio of 42:21 and 21:16, respectively (determined by GC),[14] which proved to be difficult to separate by chromatography on silica gel. The structures of (±)-**7a**, (±)-**8a**, and (±)-**10a** were assigned by comparison with their ^1H and ^{13}C NMR data described in the literature.[15] No improvement was obtained starting with the *N*-benzylpyridinium compound **6b**. It should be pointed out that 1,2,5,6- and 1,2,3,6-tetrahydropyridine isomers could be clearly identified by ^1H NMR in deuterated chloroform through their benzylic methylene signal. Thus, for 4,5-unsaturated isomers (±)-**7b**/(±)-**8b**, benzylic methylene protons appeared as a quadruplet (AB system) whereas a singlet was observed for the 3,4-unsaturated analogues (±)-**9b**/(±)-**10b**.

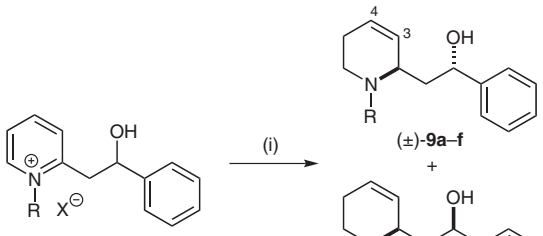
In view of this disappointing experience, we undertook a reinvestigation of this key reaction with other reducing agents, with the aim of developing a more diastereoselective and scalable process. Sodium and tetramethylammonium triacetoxyborohydride have been successfully used to reduce β-hydroxy ketones to the corresponding *anti*-diols in a diastereoselective manner, in various solvents such as acetonitrile or acetic acid.[16] We, therefore, decided to study the reduction of our β-hydroxy pyridinium compounds **6a–f** under similar conditions. The pyridini-



Scheme 3 *Reagents and conditions*: (i) $NaBH_4$, EtOH, r.t., 24 h, 85% overall (**6a**), 66% overall (**6b**).

um starting material was soluble in a mixture of dichloromethane–dimethyl sulfoxide (10:1), and reduction was achieved by treatment with excess of sodium triacetoxyborohydride after a minimum of two days at room temperature (Table 2). Under these conditions, we obtained exclusively the 3,4-unsaturated derivatives (±)-**9**/(±)-**10**. Furthermore, the major diastereoisomer was the expected amino alcohol (±)-**9** (Table 2). Attempts to reduce the reaction time by increasing the temperature resulted in the formation of colored side products by dehydration of the starting material.[17] This had already been observed in the quaternarization step when the temperature exceeded 37 °C. Purification was efficiently carried out by chromatography on silica gel to afford the desired diastereoisomers (±)-**9a–g** in ~60% yield.

Table 2 Synthesis of the 1,2,5,6-Tetrahydropyridine Derivatives (±)-**9** Using Borohydride Reduction[a]

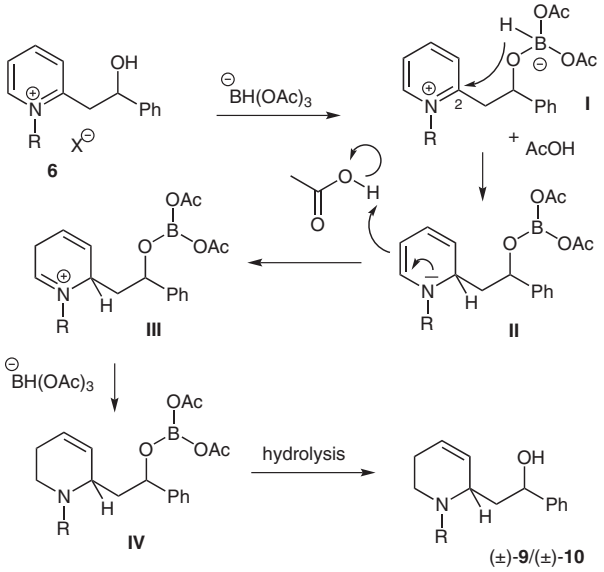


6a R = Me, X = I
6b R = Bn, X = Br
6c R = 4-$BrCH_2C_6H_4$, X = Br
6d R = 4-$NO_2CH_2C_6H_4$, X = Br
6e R = 4-$FCH_2C_6H_4$, X = Br
6f R = 4-$MeOCH_2C_6H_4$, X = Cl

Entry	Substrate	Time (d)	Ratio[b] (±)-**9**/(±)-**10**	Yield (%)
1	**6a**	2	90:10	85
2	**6a**	2	85:15	60[c]
3	**6b**	2	82:18	71
4	**6c**	4	88:12	74
5	**6d**	4	94:6	72
6	**6e**	3	87:13	83
7	**6f**	4	87:13	60

[a] Reaction conditions: (i) $NaBH(OAc)_3$ (3 to 4 equiv), CH_2Cl_2–DMSO (10:1).
[b] Determination of the diastereoisomeric ratio was achieved by ^1H NMR spectrum analysis.
[c] $NMe_4BH(OAc)_3$ was used instead of $NaBH(OAc)_3$.

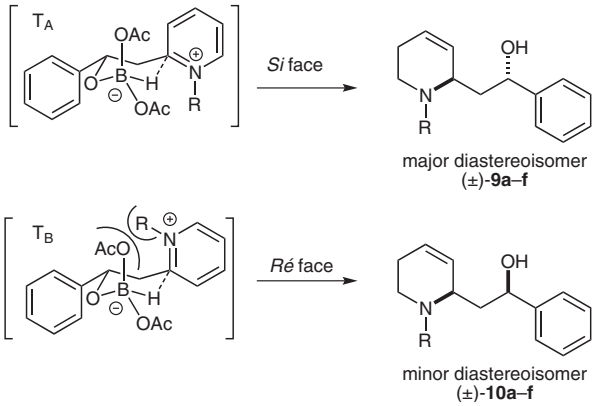
These observations led us to propose the mechanistic pathway outlined in Scheme 4. In the first step, ligand exchange between the alcohol function of **6** and the reducing agent led to intermediate **I** in which a regiospecific intramolecular transfer of hydride at C2 took place with the formation of the 1,2-dihydropyridine intermediate **II**. Then, this latter intermediate reacted with the liberated acetic acid to afford the 2,5-dihydropyridinium salt **III**, which was reduced by the second equivalent of triacetoxyborohydride to give the 3,4-unsaturated derivatives (±)-**9**/(±)-**10** via hydrolysis of intermediate **IV**. With sodium borohydride in ethanol, the intermolecular hydride addition on the pyridinium substrate prior to the intramolecular hydride delivery could explain the lack of regioselectivity of the initial reduction step and consequently the isolation of both 1,2,5,6- and 1,2,3,6-tetrahydropyridine isomers.[18]



Scheme 4

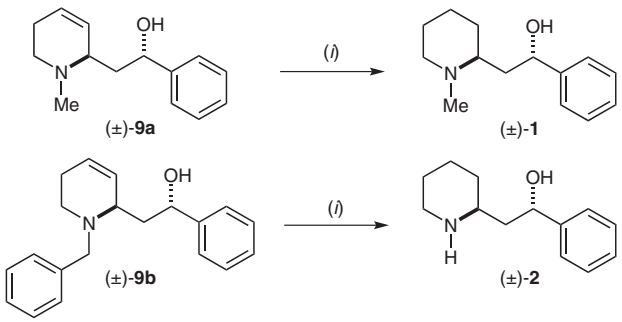
On the basis of the model proposed by Evans and co-workers,[16b] it appeared that the intramolecular hydride delivery occurred by the *Si*-face of the iminium (chairlike transition state T_A) to avoid 1,3-diaxial interaction between the acetate ligand and the R group (chairlike transition state T_B) as outlined in Scheme 5. The stereospecificity of the hydride reduction was confirmed by comparison with the literature data.[9] In contrast to the reduction of β-hydroxy ketones, with our *N*-alkylpyridinium substrates the addition of acetic acid was not necessary. As already mentioned by Evans, a slight increase in diastereoselectivity was observed using sodium instead of the tetramethylammonium counterion. Besides, with tetramethylammonium triacetoxyborohydride the reaction mixture evolved to a deep red coloration with the formation of secondary products and the desired compound **9** was isolated in lower yield (see Table 2, entry 2).

Encouraged by this result, we wanted to apply such a hydride reduction to the synthesis of norsedamine **2**, simply starting from the protonated pyridine derivative **5** in acidic conditions. However, using the same solvent mixture (CH_2Cl_2–DMSO) in the presence of acetic acid or hydrochloric acid (1 M HCl ethereal solution), no reduction occurred. Further investigations with the acetate or tosylate salts of **5** with sodium borohydride in pure acetic acid or a mixture of acetic acid–acetonitrile failed, as did using the conditions described by Katoh and co-workers:[19] basic workup gave compound **5** intact in good yields.



Scheme 5

Having determined the optimal reduction conditions, we prepared diverse analogues of (±)-sedamine [(±)-**1**] and (±)-allosedamine [(±)-**3**] (Scheme 6). First of all, treatment of the unsaturated compound (±)-**9a** under atmospheric pressure of hydrogen in the presence of Raney nickel as the catalyst afforded the expected (±)-sedamine [(±)-**1**] as the sole diastereoisomer. Surprisingly, when this latter reaction was conducted in the presence of palladium on black carbon or platinum oxide as catalyst, the expected compound (±)-**9a** was systematically isolated along with a small amount (10–15%) of (±)-allosedamine [(±)-**3**]. A possible mechanistic explanation for the presence of allosedamine **3** is the formation of an imine or iminium intermediate, via palladium- or platinum-mediated π-allylic rearrangement, which was hydrogenated in situ. However, starting from the same compound (±)-**9a** in methanolic solution, Bates and co-workers quantitatively obtained the only expected (±)-sedamine [(±)-**1**], using 10% palladium-on-carbon.[9b] Finally, we also accessed the expected racemic (±)-norsedamine [(±)-**2**] from *N*-benzyl-1,2,5,6-tetrahydropyridine derivative (±)-**9b** using Raney nickel as the catalyst under hydrogen by hydrogenation of the double bond and hydrogenolysis of the *N*-benzyl protected group.



Scheme 6 *Reagents and conditions*: (*i*) Raney Ni (50% slurry solution in H_2O, cat.), H_2 (1 atm), MeOH, 24 h, quant. [(±)-**1**], 97%[(±)-**2**].

In summary, we have devised a practical and reliable diastereoselective reduction of various *N*-alkyl-2-(2-hydroxy-2-phenylethyl)pyridinium salts on a multigram scale with sodium triacetoxyborohydride to afford original 1,2,5,6-tetrahydropyridine derivatives in a diastereoselective manner. The efficiency of this work is illustrated by the short diastereoselective synthesis of (±)-sedamine [(±)-**1**] and (±)-norsedamine [(±)-**2**] in only four steps. An extension of this methodology to various substituted aromatic aldehydes, as well as the preparation of 1,2,5,6-tetrahydropyridine derivatives for biological evaluations in the context of central nervous system diseases, will be reported in due course.

All reactions were performed using anhyd solvents and monitored by TLC (Kieselgel 60F_{254} Merck aluminum sheet) with detection by UV light and/or with ethanolic phosphomolybdic acid soln. Flash column chromatography was performed on silica gel 60 ACC 40–63 μm (SDS). Petroleum ether = PE ^{1}H and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz, respectively, on a Bruker ARX300 NMR spectrometer, referenced to TMS as an internal standard. MS and HRMS spectra were recorded at the 'Centre Commun de Spectrométrie de Masse – Claude Bernard', University of Lyon, on a Thermo-Finnigan MAT 95 XL apparatus. Mps were measured on a Stuart Scientific apparatus 7SMP3 or Kofler Heating Plate Type WME and are uncorrected.

1-Phenyl-2-(2-pyridyl)ethanol (5)

To a soln of 2-picoline (2.4 mL, 24 mmol) in anhyd THF (30 mL) cooled to –60 °C was slowly added 1.6 M *n*-BuLi in hexane (20 mL, 31.2 mmol) keeping the temperature at ca. –50 °C. The mixture was stirred at this temperature for 20 min and then benzaldehyde (5 mL, 48 mmol) in soln in anhyd THF (5 mL) was added dropwise to the red mixture at –50 °C. After 1 h the mixture completely decolored and was hydrolyzed with sat. aq NH_4Cl soln (40 mL). The compound was extracted with CH_2Cl_2, and organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. Precipitation (hexane) gave **5** (3.7 g, 81%) as a white powder; mp 111.5 °C (Lit.[11a] 110 °C); R_f = 0.2 (PE–EtOAc, 80:20).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.54 (d, *J* = 2.1 Hz, 1 H, H_{Ar}), 7.62 (t, *J* = 7.0 Hz, 1 H, H_{Ar}), 7.50–7.10 (m, 7 H, H_{Ar}), 5.17 (dd, *J* = 4.2, 8.1 Hz, 1 H, C*H*OH), 3.13 (m, 2 H, CH_2CHOH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.77 (C_2), 148.57 (C_6), 144.04 (C_{Ar}), 136.86 (C_4), 128.31 (2 C_{Ar}), 127.28 (C_{Ar}), 125.88 (2 C_{Ar}), 123.80 (C_3), 121.72 (C_5), 73.34 (CHOH), 45.66 (CH_2).

2-(2-Hydroxy-2-phenylethyl)-1-methylpyridinium Iodide (6a)

MeI (6.22 mL, 100 mmol) was added to a soln of the pyridine derivative **5** (2 g, 10 mmol) in anhyd THF (25 mL). The mixture was stirred at 37 °C for 2 d. The precipitate formed was filtered and washed with Et_2O to afford **6a** (3.2 g, 95%) as a white powder; mp 180 °C (Lit.[11a] 161–162 °C).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.98 (d, *J* = 6.0 Hz, 1 H, H_6), 8.52 (t, *J* = 8.0 Hz, 1 H, H_4), 8.10 (d, *J* = 8.0 Hz, 1 H, H_3), 7.98 (t, *J* = 6.0 Hz, 1 H, H_5), 7.50–7.30 (m, 5 H, H_{Ar}), 5.83 (d, *J* = 4.2 Hz, 1 H, OH), 5.10 (m, 1 H, C*H*OH), 4.36 (s, 3 H, NCH_3), 3.42 (m, 2 H, CH_2CHOH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 156.23 (C_2), 144.60, 142.32 (C_6, C_4), 144.01 (C_{Ar}); 129.63 (C_3), 128.24 (2 C_{Ar}), 127.54 (C_{Ar}), 125.77 (2 C_{Ar}), 125.51 (C_5), 71.18 (CHOH), 45.97 (NCH_3), 41.52 (CH_2).

1-Benzyl-2-(2-hydroxy-2-phenylethyl)pyridinium Bromide (6b)

BnBr (1.98 mL, 16.56 mmol) and KI (cat.) were added to a soln of the pyridine derivative **5** (3 g, 15 mmol) in anhyd THF (40 mL). The mixture was stirred at 37 °C for 3 d. The precipitate formed was filtered and washed with Et_2O to afford **6b** (4.9 g, 89%) as a white powder; mp 158–160 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.09 (d, J = 6 Hz, 1 H, H_6), 8.60 (t, J = 6 Hz, 1 H, H_4), 8.17 (d, J = 6 Hz, 1 H, H_3), 8.09 (t, J = 6 Hz, 1 H, H_5), 7.44–7.20 (m, 10 H, H_{Ar}), 6.12 (d, J = 15 Hz, 1 H, CH_2Ph), 6.02 (d, J = 15 Hz, 1 H, CH_2Ph), 5.92 (br s, 1 H, OH), 4.94 (dt, J = 12, 3 Hz, 1 H, C*H*OH), 3.46–3.29 (m, 2 H, CH_2CHOH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 156.05 (C_2), 146.26, 145.40 (C_6, C_4), 143.78 (C_{Ar}), 133.85 (C_{Ar}), 130.94 (C_3), 129.27 (2 C_{Ar}), 128.79 (C_{Ar}), 128.23 (2 C_{Ar}), 127.53 (C_{Ar}), 127.23 (2 C_{Ar}), 126.30 (C_5), 125.76 (2 C_{Ar}), 71.22 (*C*HOH), 60.31 (*C*H_2Ph), 41.52 (*C*H_2CH).

HRMS (ES+): m/z [M$^+$] calcd for $C_{20}H_{20}NO$: 290.1545; found: 290.1546.

1-(4-Bromobenzyl)-2-(2-hydroxy-2-phenylethyl)pyridinium Bromide (6c)

4-Bromobenzyl bromide (2.25 g, 9 mmol) and KI (cat.) were added to a soln of the pyridine derivative **5** (1.5 g, 7.5 mmol) in anhyd THF (20 mL). The mixture was stirred at 37 °C for 3 d. The precipitate formed was filtered and washed with Et_2O to afford **6c** (1.3 g). The filtrate was concentrated and the brown oil was taken up in CH_2Cl_2. The precipitate formed was filtered, and the combined solids were washed with Et_2O to give pure **6c** (3.3 g, 95%) as a white powder; mp 160–162 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.08 (d, J = 6 Hz, 1 H, H_6), 8.62 (t, J = 6 Hz, 1 H, H_4), 8.19 (d, J = 6 Hz, 1 H, H_3), 8.10 (t, J = 6 Hz, 1 H, H_5), 7.65 (d, J = 6 Hz, 2 H, H_{Ar}), 7.42–7.28 (m, 5 H, H_{Ar}), 7.22 (d, J = 6 Hz, 2 H, H_{Ar}), 6.11 (d, J = 12 Hz, 1 H, CH_2Ph), 6.02 (d, J = 12 Hz, 1 H, CH_2Ph), 5.90 (d, J = 3 Hz, 1 H, OH), 4.98 (dd, J = 3, 12 Hz, 1 H, C*H*OH), 3.43–3035 (m, 2 H, CH_2CHOH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 156.14 (C_2), 146.23, 145.50 (C_6, C_4), 143.73 (C_{Ar}), 133.22 (C_{Ar}), 133.15 (2 C_{Ar}), 130.90 (C_3), 129.75 (2 C_{Ar}), 128.24 (2 C_{Ar}), 127.56 (C_{Ar}), 126.35 (C_5), 125.78 (2 C_{Ar}), 122.14 (C_{Ar}), 71.27 (*C*HOH), 59.62 (*C*H_2Ph), 41.42 (*C*H_2CH).

HRMS (ES+): m/z [M$^+$] calcd for $C_{20}H_{19}BrNO$: 368.0650; found: 368.0651.

2-(2-Hydroxy-2-phenylethyl)-1-(4-nitrobenzyl)pyridinium Bromide (6d)

4-Nitrobenzyl bromide (9.8 g, 45 mmol) and KI (cat.) were added to a soln of the pyridine derivative **5** (3 g, 15 mmol) in anhyd THF (40 mL). The mixture was stirred at r.t. for 4 d. The mixture was concentrated in vacuo and the brown oil was taken up in CH_2Cl_2–MeOH and then diluted with a large amount of Et_2O. The precipitate formed was filtered and washed with Et_2O to afford **6d** (4.09 g, 65%) as a brown powder; mp 190–192 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.19 (d, J = 6 Hz, 1 H, H_6), 8.68 (t, J = 6 Hz, 1 H, H_4), 8.26 (d, 3 H, H_3, 2 H_{Ar}), 8.15 (t, J = 6 Hz, 1 H, H_5), 7.32–7.28 (m, 7 H, H_{Ar}), 6.40 (d, J = 12 Hz, 1 H, CH_2Ph), 6.30 (d, J = 12 Hz, 1 H, CH_2Ph), 5.93 (d, 1 H, OH), 5.01 (m, 1 H, C*H*OH), 3.43–3.35 (m, 2 H, CH_2CHOH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 156.31 (C_2), 146.54, 145.84 (C_6, C_4), 143.67 (C_{Ar}), 141.21 (C_{Ar}), 131.02 (C_3), 128.51 (2 C_{Ar}), 128.19 (2 C_{Ar}), 127.51 (C_{Ar}), 126.50 (C5), 125.81 (2 C_{Ar}), 124.16 (2 C_{Ar}), 124.00 (C_{Ar}), 71.2 (*C*HOH), 59.4 (*C*H_2Ph), 41.5 (*C*H_2CH).

HRMS (ES+): m/z [M$^+$] calcd for $C_{20}H_{19}N_2O_3$: 335.1396; found: 335.1395.

1-(4-Fluorobenzyl)-2-(2-hydroxy-2-phenylethyl)pyridinium Bromide (6e)

4-Fluorobenzyl bromide (3.3 mL, 26 mmol) and KI (cat.) were added to a soln of the pyridine derivative **5** (1.76 g, 8.8 mmol) in anhyd THF (20 mL). The mixture was stirred at r.t. for 4 d. The precipitate formed was filtered and washed with Et_2O to afford **6e** (2.05 g, 60%) as a white powder; mp 186–188 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.06 (d, J = 6 Hz, 1 H, H_6), 8.61 (t, J = 6 Hz, 1 H, H_4), 8.18 (d, J = 6 Hz, 1 H, H_3), 8.10 (t, J = 6 Hz, 1 H, H_5), 7.44–7.26 (m, 9 H, H_{Ar}), 6.10 (d, J = 18 Hz, 1 H, CH_2Ph), 6.00 (d, J = 18 Hz, 1 H, CH_2Ph), 5.93 (d, J = 3 Hz, 1 H, OH), 4.98–4.95 (m, 1 H, C*H*OH), 3.44–3.32 (m, 2 H, CH_2CHOH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 162.11 (d, $^1J_{CF}$ = 244 Hz, CF), 156.01 (C_2), 146.06, 145.36 (C_6, C_4), 143.76 (2 C_{Ar}), 130.92 (C_3), 130.00 (d, $^3J_{CF}$ = 7.5 Hz, 2 C_{Ar}), 128.22 (2 C_{Ar}), 127.51 (C_{Ar}), 126.30 (C_{Ar}), 125.81 (2 C_{Ar}), 116.15 (d, $^2J_{CF}$ = 21.75 Hz, 2 C_{Ar}), 71.17 (*C*HOH), 59.44 (*C*H_2Ph), 41.45 (*C*H_2CH).

HRMS (ES+): m/z [M$^+$] calcd for $C_{20}H_{19}FNO$: 308.1451; found: 308.1451.

2-(2-Hydroxy-2-phenylethyl)-1-(4-methoxybenzyl)pyridinium Chloride (6f)

4-Methoxybenzyl chloride (1.63 mL, 10 mmol) and KI (cat.) were added to a soln of the pyridine derivative **5** (1 g, 5 mmol) in anhyd THF (6 mL). The mixture was stirred at r.t. for 7 d. The mixture was concentrated in vacuo and the brown oil was taken up in CH_2Cl_2–MeOH and then diluted with a large amount of Et_2O. The precipitate formed was filtered and washed with Et_2O to afford **6f** (1.7 g, 95%) as a brown oil.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.10 (d, J = 6 Hz, 1 H, H_6), 8.57 (t, J = 6 Hz, 1 H, H_4), 8.15 (d, J = 6 Hz, 1 H, H_3), 8.06 (t, J = 6 Hz, 1 H, H_5), 7.45–7.31 (m, 5 H, H_{Ar}), 7.25 (d, J = 9 Hz, 2 H, H_{Ar}), 7.01 (d, J = 9 Hz, 2 H, H_{Ar}), 6.10 (d, J = 12 Hz, 1 H, CH_2Ph), 6.01 (d, J = 12 Hz, 1 H, CH_2Ph), 5.05 (m, 1 H, C*H*OH), 3.81 (s, 3 H, OCH_3), 3.57–3.43 (m, 2 H, CH_2CHOH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 159.58 (C_{Ar}), 155.93 (C_2), 145.81, 145.08 (C_6, C_4), 143.84 (C_{Ar}), 130.85 (C_{Ar}), 129.35 (2 C_{Ar}), 128.20 (2 C_{Ar}), 127.47 (C_{Ar}), 126.14 (C_5), 125.81 (2 C_{Ar}), 125.46 (C_{Ar}), 114.65 (2 C_{Ar}), 71.24 (*C*HOH), 59.90 (*C*H_2Ph), 55.24 (OMe), 41.43 (*C*H_2CH).

Reduction of Pyridinium Derivatives 6; General Procedure

The pyridinium derivative **6** was dissolved in a mixture of CH_2Cl_2–DMSO (10:1 or 8:2) and $NaBH(OAc)_3$ (4 equiv) was added. The mixture was stirred at r.t. for 2–4 d and then it was hydrolyzed with sat. aq NH_4Cl soln. The organic layer was washed with brine, dried ($MgSO_4$), and filtered and the solvent was removed under reduced pressure. Purification of the residue by column chromatography (silica gel) gave the expected compound **9**.

(±)-(1*S*)-2-[(2*R*)-1-Methyl-1,2,5,6-tetrahydropyridin-2-yl]-1-phenylethanol [(±)-9a] and (±)-(1*S*)-2-[(2*S*)-1-Methyl-1,2,5,6-tetrahydropyridin-2-yl]-1-phenylethanol [(±)-10a]

Following the general procedure and starting from **6a** (31.1g, 91.3 mmol), column chromatography (CH_2Cl_2–MeOH, 97:3) afforded the pure major compound (±)-**9a** and the pure minor compound (±)-**10a** which were both isolated as solids.

Compound (±)-9a

White solid; yield: 12.7g (64%); mp 57.8 °C; R_f = 0.3 (CH_2Cl_2–MeOH, 97:3).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.23 (m, 5 H, H_{Ar}), 5.78 (m, 1 H, H_4), 5.55 (dt, J = 9, 1.5 Hz, 1 H, H_3), 4.91 (dd, J = 9, 3 Hz, 1 H, C*H*OH), 3.23 (br d, J = 9 Hz, 1 H, H_2), 3.16 (m, 1 H, H_6), 2.74 (dd, J = 13.7, 6.0 Hz, 1 H, H_6), 2.54 (s, 3 H, NCH_3), 2.35–2.2 (m, 1 H, H_5), 1.84–1.66 (m, 3 H, H_5, CH_2CHOH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.39 (C_{Ar}), 128.20 (2 C_{Ar}), 127.67, 126.93 (C_3, C_4), 125.59 (2 C_{Ar}), 125.09 (C_{Ar}), 75.39 (CHOH), 61.17 (C_2), 43.43 (*C*H_2CHOH), 41.10 (C_6, NCH_3), 18.46 (C_5).

HRMS: m/z [M + H$^+$] calcd for $C_{14}H_{20}NO$: 218.1545; found: 218.1545.

Compound (±)-10a

White solid; yield: 1.5g (8%); mp 97.2 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.22 (m, 5 H, H_{Ar}), 5.89 (m, 1 H, H_4), 5.46 (m, 1 H, H_3), 4.92 (dd, *J* = 7.56, 1.74 Hz, 1 H, C*H*OH), 3.08 (m, 1 H, H_2), 2.87 (m, 1 H, H_6), 2.46 (s, 3 H, NCH_3), 2.35–2.29 (m, 2 H, H_5, H_6), 2.06 (ddd, *J* = 15.81, 7.59, 2.79, Hz, 1 H, CH_2CHOH), 1.97 (m, 1 H, H_5), 1.58 (ddd, *J* = 11.01, 3.03, 1.86 Hz, 1 H, CH_2CHOH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 145.31 (C_{Ar}), 128.31 (C_{Ar}), 128.17 (2 C_{Ar}), 126.99, 126.78 (C_3, C_4), 125.60 (2 C_{Ar}), 71.89 (CHOH), 61.38 (C_2), 51.28 (CH_2), 43.31 (NCH_3), 39.98 (CH_2), 24.79 (CH_2).

(±)-(1*S*)-2-[(2*R*)-1-Benzyl-1,2,5,6-tetrahydropyridin-2-yl]-1-phenylethanol [(±)-9b]

Following the general procedure and starting from **6b** (2.5 g, 6.75 mmol), column chromatography (CH_2Cl_2–Et_2O, 95:5) afforded (±)-**9b** (1.2 g, 60%) as a colorless oil which rapidly turned brown; R_f = 0.66 (CH_2Cl_2–MeOH, 99:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50–7.20 (m, 10 H, H_{Ar}), 5.85 (m, 1 H, H_4), 5.59 (m, 1 H, H_3), 4.74 (dd, *J* = 10.5, 1.5 Hz, 1 H, C*H*OH), 3.86 (s, 2 H, CH_2Ar), 3.38 (br d, *J* = 11.4 Hz, 1 H, H_2), 3.17 (m, 1 H, H_6), 2.76 (dd, *J* = 14.1, 6.0 Hz, 1 H, H_6), 2.32 (m, 1 H, H_5), 1.84–1.78 (m, 2 H, H_5, CH_2CHOH), 1.65 (dt, *J* = 14.7, 2.4 Hz, 1 H, CH_2CHOH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.98 (C_{Ar}), 137.87 (C_{Ar}), 129.37 (2 C_{Ar}), 128.58 (2 C_{Ar}), 128.16 (2 C_{Ar}), 127.83 (C_{Ar}), 127.50 (C_{Ar}), 126.95 (C_{Ar}), 125.55 (2 C_{Ar}), 125.22 (C_4), 75.24 (CHOH), 59.17 (C_2), 57.15 (*C*H_2Ar), 41.34 (*C*H_2CHOH), 40.43 (C_6), 18.58 (C_5).

HRMS (CI): *m*/*z* [M + H^+] calcd for $C_{20}H_{24}NO$: 294.1858; found: 294.1858.

(±)-(1*S*)-2-[(2*R*)-1-(4-Bromobenzyl)-1,2,5,6-tetrahydropyridin-2-yl]-1-phenylethanol [(±)-9c]

Following the general procedure and starting from **6c** (1.25 g, 2.7 mmol), column chromatography (CH_2Cl_2–Et_2O, 95:5 to 80:20) afforded pure (±)-**9c** (0.57 g, 56%) as a colorless oil which rapidly turned brown; R_f = 0.75 (CH_2Cl_2–MeOH, 99:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.00 (m, 9 H, H_{Ar}), 5.83 (m, 1 H, H_4), 5.58 (m, 1 H, H_3), 4.72 (dd, *J* = 10.5, 2.1 Hz, 1 H, C*H*OH), 3.81 (s, 2 H, CH_2Ar), 3.38 (br d, *J* = 12 Hz, 1 H, H_2), 3.17 (m, 1 H, H_6), 2.77 (dd, *J* = 14.1, 5.7 Hz, 1 H, H_6), 2.33 (m, 1 H, H_5), 1.86–1.75 (m, 2 H, H_5, CH_2CHOH), 1.65 (dt, *J* = 14.7, 2.7 Hz, 1 H, CH_2CHOH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.84 (C_{Ar}), 136.92 (C_{Ar}), 131.74 (2 C_{Ar}), 131.05 (2 C_{Ar}), 128.22 (2 C_{Ar}), 127.72 (C_{Ar}), 127.03 (C_{Ar}), 125.55 (2 C_{Ar}), 125.24 (C_4), 121.45 (C_{Ar}), 75.24 (CHOH), 59.16 (C_2), 56.52 (*C*H_2Ar), 41.34 (*C*H_2CHOH), 40.60 (C_6), 18.60 (C_5).

HRMS (CI): *m*/*z* [M + H^+] calcd for $C_{20}H_{23}BrNO$: 372.0963; found: 372.0962.

(±)-(1*S*)-2-[(2*R*)-1-(4-Nitrobenzyl)-1,2,5,6-tetrahydropyridin-2-yl]-1-phenylethanol [(±)-9d]

Following the general procedure and starting from **6d** (1.6 g, 3.8 mmol), column chromatography (PE–Et_2O, 50:50) afforded (±)-**9d** (0.82 g, 63%) as a brown oil; R_f = 0.90 (CH_2Cl_2–MeOH, 99:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.22 (d, *J* = 6.0 Hz, 2 H, H_{Ar}), 7.60 (d, *J* = 6.0 Hz, 2 H, H_{Ar}) 7.36–7.22 (m, 5 H, H_{Ar}), 5.88 (m, 1 H, H_4), 5.62 (m, 1 H, H_3), 4.73 (dd, *J* = 12.00, 3.00 Hz, 1 H, C*H*OH), 3.95 (s, 2 H, CH_2Ar), 3.35 (br d, *J* = 9.0 Hz, 1 H, H_2), 3.21 (ddd, *J* = 4.92, 11.82, 14.1 Hz, 1 H, H_6), 2.74 (dd, *J* = 14.13, 5.76 Hz, 1 H, H_6), 2.31 (m, 1 H, H_5), 1.86–1.75 (m, 2 H, H_5, CH_2CHOH), 1.70 (dt, *J* = 14.76, 2.73 Hz, 1 H, CH_2CHOH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.48 (C_{Ar}), 145.55 (C_{Ar}), 144.58 (C_{Ar}), 130.04 (2 C_{Ar}), 128.27 (2 C_{Ar}), 127.56 (C_{Ar}), 127.14 (C_{Ar}), 125.52 (2 C_{Ar}), 125.28 (C_4), 123.87 (2 C_{Ar}), 75.17 (CHOH), 59.49 (C_2), 56.59 (*C*H_2Ar), 41.39 (*C*H_2CHOH), 41.04 (C_6), 18.72 (C_5).

HRMS (CI): *m*/*z* [M + H^+] calcd for $C_{20}H_{23}N_2O_3$: 339.1710; found: 339.1709.

(±)-(1*S*)-2-[(2*R*)-1-(4-Fluorobenzyl)-1,2,5,6-tetrahydropyridin-2-yl]-1-phenylethanol [(±)-9e]

Following the general procedure and starting from **6e** (1.5 g, 3.9 mmol), column chromatography (CH_2Cl_2–Et_2O, 95:5 to 80:20) afforded (±)-**9e** (0.71 g, 60%) as a colorless oil; ratio (±)-**9e**/(±)-**10e**, 87:13; R_f = 0.54 (CH_2Cl_2–MeOH, 99:1).

^{1}H NMR (300 MHz, $CDCl_3$): 7.40–7.22 (m, 7 H, H_{Ar}), 7.04 (t, *J* = 9.0 Hz, 2 H, H_{Ar}), 5.83 (m, 1 H, H_4), 5.58 (m, 1 H, H_3), 4.73 (d, *J* = 9 Hz, 1 H, C*H*OH), 3.83 (s, 2 H, CH_2Ar), 3.37 (br d, *J* = 10.35 Hz, 1 H, H_2), 3.21 (ddd *J* = 14.04, 11.85, 4.80 Hz, 1 H, H_6), 2.74 (dd, *J* = 14.04, 5.67 Hz, 1 H, H_6), 2.30 (m, 1 H, H_5), 1.90–1.75 (m, 2 H, H_5, CH_2CHOH), 1.67 (dt, *J* = 14.67, 2.52 Hz, 1 H, CH_2CHOH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.24 (d, $^1J_{CF}$ = 24.5 Hz, CF), 144.88 (C_{Ar}), 133.6 (C_{Ar}), 130.90 (d, $^1J_{CF}$ = 8.25 Hz, 2 C_{Ar}), 128.21 (2 C_{Ar}), 127.76 (C_{Ar}), 127.01 (C_{Ar}), 125.56 (2 C_{Ar}), 125.24 (C_4), 115.45 (d, $^2J_{CF}$ = 21 Hz, 2 C_{Ar}), 75.27 (CHOH), 59.04 (C_2), 56.36 (*C*H_2Ar), 41.35 (*C*H_2CHOH), 40.51 (C_6), 18.59 (C_5).

HRMS (CI): *m*/*z* [M + H^+] calcd for $C_{20}H_{23}FNO$: 312.1764; found: 312.1763.

(±)-(1*S*)-2-[(2*R*)-1-(4-Methoxybenzyl)-1,2,5,6-tetrahydropyridin-2-yl]-1-phenylethanol [(±)-9f]

Following the general procedure and starting from **6f** (1.7 g, 4.8 mmol), column chromatography (CH_2Cl_2–Et_2O, 95:5 to 90:10) afforded (±)-**9f** (0.74 g, 50%) as a brown oil; R_f = 0.34 (CH_2Cl_2–MeOH, 99:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.21 (m, 7 H, H_{Ar}), 6.89 (d, *J* = 8.58 Hz, 2 H, H_{Ar}), 5.83 (m, 1 H, H_4), 5.58 (m, 1 H, H_3), 4.71 (br d, *J* = 10.17 Hz, 1 H, C*H*OH), 3.82 (s, 5 H, CH_2Ar, OMe), 3.39 (br d, *J* = 9 Hz, 1 H, H_2), 3.17 (ddd *J* = 13.7, 11.82, 4.92 Hz, 1 H, H_6), 2.77 (dd, *J* = 13.7, 5.04 Hz, 1 H, H_6), 2.32 (m, 1 H, H_5), 1.90–1.68 (m, 3 H, H_5, CH_2CHOH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.01 (C_{Ar}), 145.05 (C_{Ar}), 130.55 (2 C_{Ar}), 129.91 (C_{Ar}), 128.17 (2 C_{Ar}), 127.86 (C_{Ar}), 126.93 (C_{Ar}), 125.58 (2 C_{Ar}), 125.24 (C_4), 113.94 (2 C_{Ar}), 75.24 (CHOH), 58.84 (C_2), 56.43 (*C*H_2Ar), 55.27 (OCH_3), 41.34 (*C*H_2CHOH), 40.44 (C_6), 18.61 (C_5).

HRMS (CI): *m*/*z* [M + H^+] calcd for $C_{21}H_{26}NO_2$: 324.1964; found: 324.1964.

(±)-Sedamine [(±)-1]

A catalytic amount of Raney Ni (50% slurry soln in water washed with MeOH under argon) was added to (±)-**9a** (0.2 g, 0.92 mmol) in MeOH (5 mL). The resulting mixture was stirred under an atmosphere of H_2 (balloon) for 22 h. Then, the mixture was filtered and the solvent evaporated in vacuo to afford quantitatively (±)-sedamine [(±)-**1**] (0.2 g) as a beige solid; mp 87–90 °C (Lit.[11a] 90 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.15 (m, 5 H, H_{Ar}), 4.79 (dd, *J* = 10.5, 2.7 Hz, 1 H, C*H*OH), 3.03–2.95 (m, 1 H, H_6), 2.89–2.69 (m, 1 H, H_2), 2.50–2.35 (m, 1 H, H_6), 2.40 (s, 3 H, NCH_3), 2.12–2.00 (m, 1 H, CH_2CHOH), 1.82–1.20 (m, 7 H, H_3, H_4, H_5, CH_2CHOH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.26 (C_{Ar}), 127.99 (2 C_{Ar}), 126.75 (C_{Ar}), 125.34 (2 C_{Ar}), 73.21 (CHOH), 60.64 (C_2), 52.21 (C_6), 40.13 (NCH_3), 10.06 (*C*H_2CHOH), 26.31, 22.28, 21.21 (C_3, C_4, C_5).

(±)-Norsedamine [(±)-2]

As described above for (±)-sedamine [(±)-**1**], (±)-**9b** (0.2 g, 0.68 mmol) in MeOH (4 mL) was stirred under an atmosphere of H_2 (balloon) for 22 h to give norsedamine [(±)-**2**] (0.135 g, 97%) as a white solid; mp 90.6 °C (Lit.[20] 92–93 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.25 (m, 5 H, H_{Ar}), 4.96 (dd, *J* = 10.62, 2.55 Hz, 1 H, C*H*OH), 3.11 (dt, *J* = 13.5, 2.0 Hz, 1 H, H_2), 2.92 (tt, *J* = 10.6, 2.4 Hz, 1 H, H_6), 2.68 (ddd, *J* = 13.5, 11.9, 2.9 Hz, 1 H, H_6), 1.90–1.05 (m, 8 H, H_3, H_4, H_5, CH_2CHOH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.25 (C_{Ar}), 128.24 (2 C_{Ar}), 126.99 (C_{Ar}), 125.57 (2 C_{Ar}), 75.55 (CHOH), 58.37 (C_2), 45.98.21 (C_6), 45.13, 34.26, 27.32, 24.46 (C_3, C_4, C_5, *C*H_2CHOH).

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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References

(1) Marion, L. *Can. J. Res.* **1945**, *23B*, 165.
(2) Gupta, R. N.; Spenser, I. D. *Can. J. Chem.* **1967**, *45*, 1275.
(3) Wieland, H.; Koschara, E. D.; Renz, J.; Schwarze, W.; Linde, W. *Justus Liebigs Ann. Chem.* **1939**, *540*, 103.
(4) Damaj, M. J.; Patrick, G. S.; Creasy, K. R.; Martin, B. R. *J. Pharmacol. Exp. Ther.* **1997**, *282*, 410.
(5) Flammia, D.; Dukat, M.; Damay, M. I.; Martin, B.; Glennon, R. A. *J. Med. Chem.* **1999**, *42*, 3726.
(6) Terry, A. V. Jr.; Williamson, R.; Gattu, M.; Beach, J. W.; McCurdy, C. R.; Sparks, J. A.; Pauly, J. R. *Neuropharmacology* **1998**, *37*, 93.
(7) Watson, P. S.; Jiang, B.; Scott, B. *Org. Lett.* **2000**, *2*, 3679.
(8) (a) Bates, R. W.; Sa-Ei, K. *Tetrahedron* **2002**, *58*, 5957. (b) Felpin, F.-X.; Lebreton, J. *Tetrahedron* **2004**, *60*, 10127.
(9) (a) Felpin, F.-X.; Lebreton, J. *J. Org. Chem.* **2002**, *67*, 9192. (b) Bates, R. W.; Nemeth, J. A.; Snell, R. H. *Synthesis* **2008**, 1033; and literature cited therein.
(10) Felpin, F.-X.; Lebreton, J. *Tetrahedron Lett.* **2002**, *43*, 225.
(11) (a) Beyerman, H. C.; Eveleens, W.; Muller, Y. M. F. *Recl. Trav. Chim. Pays-Bas* **1956**, *75*, 63. (b) Beyerman, H. C.; Eenshuistra, J.; Eveleens, W.; Zweistra, A. *Recl. Trav. Chim. Pays-Bas* **1959**, *78*, 43.
(12) Recent reviews: (a) Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, *67*, 3693. (b) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953. (c) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701. (d) Escolano, C.; Amat, M.; Bosch, J. *Chem. Eur. J.* **2006**, *12*, 8198.
(13) For a review on this topic, see: Felpin, F.-X.; Lebreton, J. *Curr. Org. Synth.* **2004**, *1*, 83.
(14) The diastereoisomeric ratio was determined by GC analysis [Optima 3 column (Macherey-Nagel), 80 °C, 1 min, 12 °C/min, 250 °C, 1 min, 12 °C/min, 300 °C]: t_R = 19.8 min [(±)-**10a**; 16%); 21.08 min ((±)-**9a**; 21%); 20.88 and 23.40 min [(±)-**7a** and (±)-**8a**, 42% and 21%, respectively].
(15) (a) For compounds 7a and 8a, see: Compère, D.; Marazano, C.; Das, B. C. *J. Org. Chem.* **1999**, *64*, 4528. (b) For compound **10a**, see ref. 9b.
(16) (a) Dondoni, A.; Fantin, G.; Fogagnolo, M. *Tetrahedron Lett.* **1989**, *30*, 6063. (b) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.
(17) Jedrzejewska, B.; Kabatc, J.; Pietrzak, M.; Paczkowski, J. *Dyes Pigm.* **2003**, *58*, 47.
(18) (a) For a very interesting overview of asymmetric hydrogenation of aromatic compounds including pyridines, see: Glorius, F. *Org. Biomol. Chem.* **2005**, *3*, 4171. (b) For more specific preparation of tetrahydropyridine derivatives in this context, see: Legault, C.; Charette, A. B. *J. Am. Chem. Soc.* **2003**, *125*, 6360.
(19) Katoh, T.; Kirihara, M.; Nagata, Y.; Kobayashi, Y.; Arai, K.; Minami, J.; Terashima, S. *Tetrahedron Lett.* **1993**, *34*, 5747.
(20) Tirel, P.-J.; Vaultier, M.; Carrié, R. *Tetrahedron Lett.* **1989**, *30*, 1947.