Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Synthesis of Piperidine Derivatives by Reduction of Pyridinium Salts

Zilong Tang [a b], Joelle Mayrargue [a] & Mouad Alami [a]

[a] Faculty of Pharmacy, Department of Chemistry, University of Paris-Sud, Chatenay-Malabry, Cedex, France

[b] School of Chemistry and Chemical Engineering, Hunan Provincial University Key Laboratory of QSAR/QSPR, Hunan University of Science and Technology, Xiangtan, P. R. China

Published online: 05 Oct 2007.

To cite this article: Zilong Tang , Joelle Mayrargue & Mouad Alami (2007): Synthesis of Piperidine Derivatives by Reduction of Pyridinium Salts, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 37:19, 3367-3379

To link to this article: http://dx.doi.org/10.1080/00397910701483944

Synthetic Communications®, 37: 3367–3379, 2007

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910701483944

Synthesis of Piperidine Derivatives by Reduction of Pyridinium Salts

Zilong Tang
Faculty of Pharmacy, Department of Chemistry, University of Paris-Sud, Chatenay-Malabry, Cedex, France and School of Chemistry and Chemical Engineering, Hunan Provincial University Key Laboratory of QSAR/QSPR, Hunan University of Science and Technology, Xiangtan, P. R. China

Joelle Mayrargue, and Mouad Alami
Faculty of Pharmacy, Department of Chemistry, University of Paris-Sud, Chatenay-Malabry, Cedex, France

Abstract: Piperidine derivatives **1a**–**e** and **2a**–**f** have been prepared by the reduction of 3- and 4-substituted pyridinium salts with $NaBH_4$ in moderate to excellent yields. The reactions regioselectively give 1,2,5,6-tetrahydropyridines, and the yields depend greatly upon the nature of substituents on the phenyl ring and on the nitrogen atom, the nature and the position of the substituents on the pyridyl ring, and the chain length between the aryloxy and the pyridyl groups.

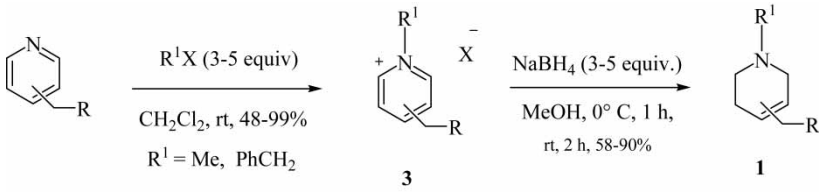
Keywords: peperidine, pyridinium salt, reduction, synthesis

Functionalized piperidines are common substructures found in natural products, and many piperidine-containing compounds have bioactivity.[1] In

Received in P. R. China October 26, 2006
Address correspondence to Joelle Mayrargue, Faculty of Pharmacy, Department of Chemistry, University of Paris-Sud, 5, rue Jean Baptiste Clement 92296, Chatenay-Malabry, Cedex, France. E-mail: joelle.mayrargue@chimorg.upsud.fr or Zilong Tang, Department of Chemistry, Faculty of Pharmacy, University of Paris-Sud, 5, rue Jean-Baptiste Clement 92296, Chatenay-Malabry, Cedex, France and School of Chemistry and Chemical Engineering, Hunan University of Science and Technology, Xiangtan, 411201, P. R. China. E-mail: zltang67@yahoo.com.cn

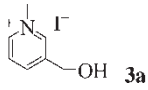
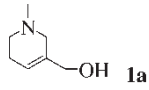
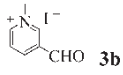
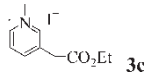
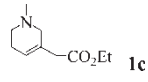
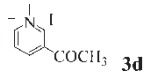
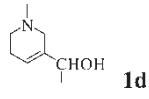
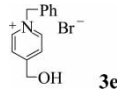
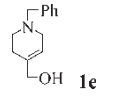
a search for new ligands for the opioid receptor-like (ORL1) receptor that was recently discovered, a fourth member of the classical μ, δ, and κ opioid receptor family,[1f–1h] we had to prepare key intermediate piperidines derivatives **1** and **2**. In the literature, there are various methods for the preparation of six-membered nitrogen heterocycles.[2] Aza–Diels–Alder reaction is often used to form six-membered nitrogen heterocycles and mostly applies to the reactions of dienes with imines. Recently, ring-closing metathesis (RCM)[2c] has provided a reliable synthetic method for the synthesis of unsaturated piperidines. However, examples of RCM where one of the olefins is directly connected to the nitrogen atom are rare. In addition, the full reduction of pyridines by hydrogenation and the partial reduction of pyridines using $NaBH_4$ provide direct and very useful synthetic tools for the generation of piperidines.[2a] There were also a few reports on the reduction pyridinium salts to tetrahedropyridines in the literature.[3] The advantage of these sequences is that the heterocyclic ring is already present. However, less attention has been paid to the position and the nature of substituents on the pyridyl ring and the substituents on the nitrogen atom. We thus adopted the reduction of 3- or 4-substituted N-alkylpyridinium salts with $NaBH_4$ to prepare piperidines derivatives **1** and **2** and investigated the effect of substituents on the reduction.

The synthetic route to unsaturated piperidines derivatives **1** is shown in Scheme 1. Initially, intermediate pyridinium salts **3** were easily prepared in 48–99% yields (Table 1) by N-alkylation of the corresponding pyridines in dichloromethane at room temperature. Then, the reduction of substituted pyridinium salts **3** with $NaBH_4$ was easily achieved in methanol to regioselectively give 1,2,5,6-tetrahydropyridines **1a**,[4] **1c**, **1d**,[5] and **1e**[6] in moderate to excellent yields. No other regioselective reduction products were found. It can be seen from Table 1 that pyridinium salts with a substituent at position 4 gave relatively higher yield than those with a substituent at position 3. The carbonyl groups in **3b** and **3d** were also reduced at the same time, whereas the ester group in **3c** remained unchangeable under the reaction conditions. (For the preparation of ethyl 2-(yridine-3-yl) acetate, precursor to compound **3c**, see Ref. 9.) However, the yield of the reduction of **3a** giving compound **1a** is higher than that of **3b** with a carbonyl group (entries 1 vs. 2).



Scheme 1.

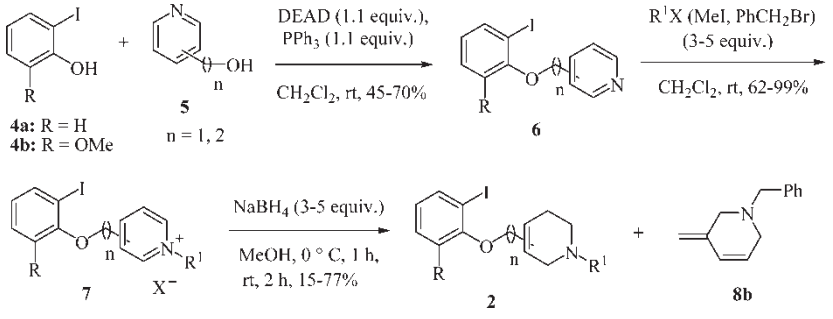
Table 1. Results of the alkyllation of pyridines and the reduction of pyridinium salts **3**

Entry	Time (h)[a]	Pyridinium salt	Yield (%)	Piperidine	Yield (%)[b]
1	12	 **3a**	90	 **1a**	83
2	48	 **3b**	48		65
3	12	 **3c**	85	 **1c**	58
4	48	 **3d**	99	 **1d**	88
5	24	 **3e**	92	 **1e**	90

[a]Time designed for the N-alkylation of pyridines.

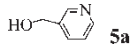
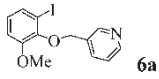
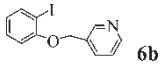
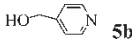
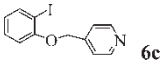
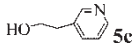
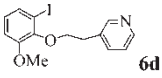
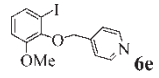
[b]$NaBH_4$ added at 0°C, and reductions stirred in methanol at 0°C for 1 h and at room temperature (rt) for 2 h.

The sequence for the preparation of 3- or 4-aryloxyalkyl unsaturated piperidines derivatives **2** is outlined in Scheme 2. The intermediate 3- or 4-aryloxyalkyl pyridines **6a**–**e** were prepared by the Mitsunobu reaction[7] of substituted phenols **4a**,[3e,8] **4b** with pyridylalkyl alcohols **5a**, **5b**, and **5c**[9] in the presence of Ph_3P and diethyl azodicarboxylate (DEAD) in dry dichloromethane at room temperature. It is seen clearly from Table 2 that the reaction gave the desired ethers **6a**–**e** in moderate to good yields, and the



Scheme 2.

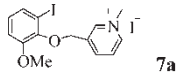
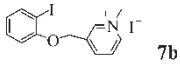
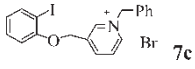
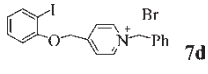
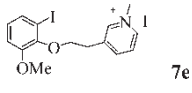
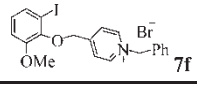
Table 2. Results of Mitsunobu reactions of phenols **4a**–**b** and alcohols **5a**–**c**

Entry	Phenols	Alcohols	Time (h)	Product	Yield (%)
1	**4a**	 **5a**	8	 **6a**	58
2	**4b**	**5a**	24	 **6b**	45
3	**4b**	 **5b**	24	 **6c**	47
4	**4a**	 **5c**	8	 **6d**	70
5	**4a**	**5b**	24	 **6e**	67

yields of **6a**, **6d**, **6e**[3e] containing a methoxy group were higher than those of **6b** and **6c** (entries 1, 4 vs. 2, 3), probably because of the positive induction of the methoxy group.

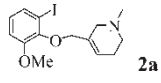
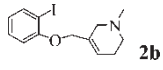
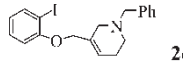
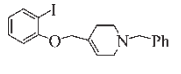
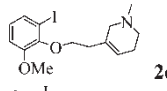
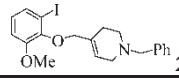
Similarly, pyridinium salts **7a**–**f** were prepared in moderate to excellent yields (Table 3) by N-alkylations of the obtained aryloxyalkyl pyridines **6a**–**e** at room temperature in dichloromethane.

Table 3. Results of N-alkylations of aryloxyalkyl pyridine **6a**–**e**

Entry	Reactant	Time (h)	Product	Yield (%)
1	**6a**	24	 **7a**	80
2	**6b**	24	 **7b**	74
3	**6b**	48	 **7c**	62
4	**6c**	24	 **7d**	85
5	**6d**	16	 **7e**	90
6	**6e**	16	 **7f**	90

Using the method described previously, we first tried to reduce 3-aryloxyalkyl pyridinium salt **7a** with $NaBH_4$ in methanol. When $NaBH_4$ was added at room temperature and the reaction was stirred at the same temperature for 3 h, compound **4a** was obtained in 90% yield together with only a trace of the expected product 1,2,5,6-tetrahydropyridines **2a**. The yield of **4a** decreased to 58% when the reaction was carried out at 0°C, and **2a** was found in 10% yield (entry 2, Table 4). The attempt to use $NaBH_3(CN)$ as a base failed to improve the reaction. However, the reduction of **7b** without a methoxy group on the phenyl ring gave **2b** in 32% yield (entry 3) at room temperature, although compound **4b** was isolated in 40% yield. While the reaction was carried out at 0°C, the yield of **2b** was further raised to 36% (entry 4) and the yield of **4b** diminished to 29%. Furthermore, when the methyl group connected to the nitrogen atom was replaced with a benzyl group, the yield of the desired product 1,2,5,6-tetrahydropyridines **2c** increased to 41% (entry 5), albeit the decoupling compound **4b** was still generated in 21% yield. Interestingly, another decoupling product **8b** (see Scheme 2) was also obtained in 24% yield. When the aryloxyalkyl group on the pyridyl ring is

Table 4. Results of the reduction of aroxyalkyl pyridiniums **7a–e**

Entry	Reactant	Product	Yield[a] (%)	Compound 4 (yield, %)
1	**7a**	 **2a**	Trace[b]	**4a** (90)
2	**7a**	**2a**	10	**4a** (58)
3	**7b**	 **2b**	32[b]	**4b** (40)
4	**7b**	**2b**	36	**4b** (29)
5	**7c**	 **2c**	41	**4b** (24)
6	**7d**	 **2d**	77	—
7	**7e**	 **2e**	64	—
8	**7f**	 **2f**	75	—

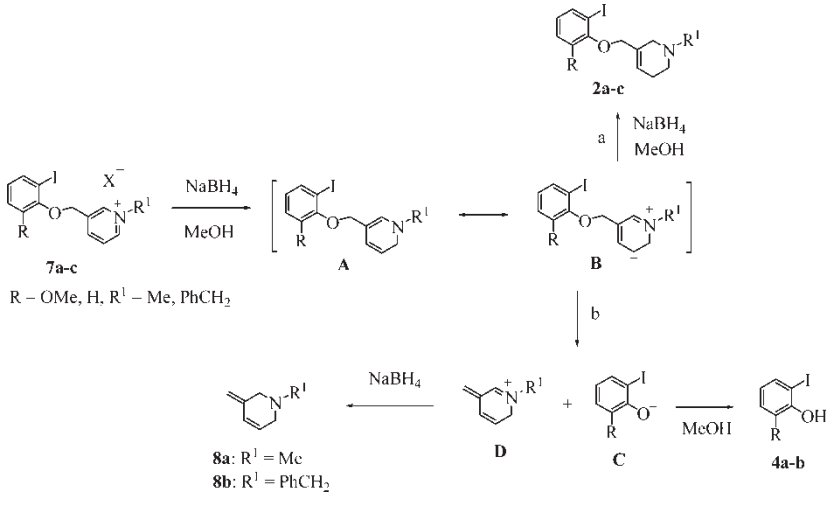
[a]$NaBH_4$ added at 0°C, and reaction stirred in methanol at 0°C for 1 h and at rt for 2 h.
[b]$NaBH_4$ added at rt, and reaction carried out at rt for 3 h.

at position 4, the yields of the reduction were raised to 75–77% (entries 6, 8), and no decoupling products **4a**, or **4b** were found. Likewise, when there are two methylene groups between the aryloxy and the pyridyl groups, the yield of the reduction of compound **7e** was 64% (entry 7) without the formation of compound **4a**, although there is a methoxy group on the phenyl ring and a substituent at position 3 of the pyridyl ring. Generally, the yields of all the present cases are relatively lower than those of the reduction of the pyridinium salts **3** with hydoxymethyl or carbonyl groups.

Alternatively, compound **2a** was prepared in 37% yield by Mitsunobu reaction of **4a** with **1a**.

To the best of our the knowledge, the decoupling reactions of **7a–c** are unprecedented. On the basis of these results, a plausible mechanism for the decoupling reactions of **7a–c** could be proposed and is shown in Scheme 3. The reduction of **7a–c** by $NaBH_4$ gave intermediate **A**, which can be transformed into **B** by resonation. A further reduction of the form **B** in methanol gave 1,2,3,6-tetrahydropyridines **2a–c** (route a). However, a decomposition of intermediate **B** to **C** and iminium **D** could also operate (route b). Protonation of **C** in methanol yielded **4a** and **b**. Further reduction of the iminium **D** by $NaBH_4$ afforded aminodiene **8**. The possibility of route b was justified by the isolation of aminodiene **8b**. Indeed, the decomposition of intermediate **B** competed with the reduction. The reaction of **B** following route a or b depended on substitutents on the phenyl ring and on the nitrogen atom, the chain length of the alkyl between the aryloxy and the pyridyl ring, and the reaction temperature.

In conclusion, piperidines derivatives **1a–e** and **2a–f** were prepared by the reduction of 3- or 4-substituted pyridinium salts with $NaBH_4$ in moderate to excellent yields. The reactions regioselectively gave 1,2,5,6-tetrahydropyridines,



Scheme 3. Possible mechanism for the decoupling reactions of **7a–c**.

and the yields depended greatly upon the nature of substituents on the phenyl ring and on the nitrogen atom, the nature and the position of substituents on the pyridyl ring, the chain length between the aryloxy and the pyridyl groups. For pyridinium salts with an aryloxyalkyl at position 4 of the pyridyl ring, the reaction gave relatively higher yield than those with an aryloxyalkyl at position 3. Likewise, when there are two methylene groups between the aryloxy and the pyridyl groups, the reduction gave good yields even if there is a methoxy group on the phenyl ring and an aryloxyalkyl at position 3 of the pyridyl ring. A possible mechanism for the unprecedented decoupling reactions of **7a–c** was also proposed. Apparently, the advantage of this sequence is that the heterocyclic ring is already present, and the C═C double bond in the piperidine ring can be further functionalized.

The Mitsunobu reaction of **1a–e** and cyclization of **2a–f** to heterocycles, as well as the bioactivity of the heterocycles, will be reported latter.

EXPERIMENTAL

General Information

All reactions requiring anhydrous or inert conditions were carried out under an atmosphere of dried argon in flame-dried glassware. All solvents were dried by standard procedure and freshly distilled. Infrared spectra were recorded on a Bruker Vector22 with Golden Gate. ^{1}H NMR spectra were recorded on a Bruker ARX 200-MHz sonde QNP (H, C, F, P) and Avance 400-MHz sonde H-BB with gradient Z. ^{13}C NMR spectra were recorded at 50 and 100 MHz. Chemical shifts (δ) are given relative to Me_4Si (0 ppm, ^{1}H) or $CDCl_3$ (77.0 ppm, ^{13}C). Mass spectra were recorded on Varian MAT-44 or Finnigan MAT-TSQ 70 spectrometers. Thin-layer chromatographic (TLC) analyses were performed on Merck 60 F254 silica-gel plates (coated on aluminium). Flash chromatograph separations were performed using Merck 60 40 to 63-μm silica. Compound **4a** was prepared according to Refs. 3e and 8 and ethyl 2-(pyridine-3-yl) acetate and compound **5c** according to Ref. 9.

Synthesis of Piperidine Derivatives 1a–e

General Procedure for the Preparation of **3a–e**

To a 250-ml flask with a stirring bar, 3.0 g of 3-hydroxymethylpyridine (27 mmol), 8.6 mL of MeI (140 mmol), and 100 mL of CH_2Cl_2 were added. The mixture was stirred at room temperature for 12 h until the disappearance of 3-hydroxymethylpyridine, checked by TLC. The solid formed was filtered and washed with dichloromethane. The crude product was recrystallized with MeOH/petroleum ether to give the pure product **3a** (yield: 90%).

General Procedure for the Preparation of **1a–e** by Reduction of **3a–e**

Compound **3a** (6.05 g, 24 mmol) was dissolved in 20 mL of MeOH, then 3.65 g of sodium borohydride (96 mmol) was added portionwise at 0°C. The mixture was continued to stir at 0°C for 1 h and then at room temperature for 2 h. The solvent was evaporated under reduced pressure, then 5 mL water was added, and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatograph to afford 2.53 g of product **1a**.

Data

(5-Hydroxymethyl)-1-methyl-1,2,5,6-tetrahydropyridine **1a**

Viscous oil, 83%. ^{1}H NMR (200 MHz, $CDCl_3$): 5.61–5.69 (m, 1H, =CH), 3.97 (s, 2H, OCH_2), 3.61 (s (br), 1H, OH), 2.93 (s, 2H), 2.47 (t, $J = 5.9$ Hz, 2H), 2.34 (s, 3H, NMe), 2.15–2.25 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): 137.05 (=C), 118.84 (=CH), 63.76 (OCH_2), 54.66, 51.68, 45.11 (NMe), 25.34; IR: 3193, 2097, 2841, 2789, 1460, 12888, 1261, 1115, 1014, 831 cm^{-1}. MS (EI, 70 eV): 127 $[M]^+$.

Ethyl 2-(1-Methyl-1,2,5,6-tetrahydropyridin-5-yl) Acetate **1c**

Viscous oil, 58%. ^{1}H NMR (200 MHz, $CDCl_3$): 5.58–5.60 (m, 1H), 4.00 (q, $J = 6$ Hz, 2H, OCH_2), 2.81 (s, 2H), 2.78 (s, 2H), 2.30 (t, $J = 4.5$ Hz, 2H), 2.20 (s, 3H, NMe), 2.07–2.09 (m, 2H), 1.13 (t, $J = 6$ Hz, 3H, Me). ^{13}C NMR (50 MHz, $CDCl_3$): 170.89 (C=O), 129.23 (=C), 123.12 (=CH), 60.29, 56.81, 51.14, 45.41 (NMe), 40.99, 25.79, 13.94 (Me). MS (EI, 70 eV): 183 $[M]^+$. HRMS-EI: calculated for $C_{10}H_{17}NO_2$: 183.1259; found: 183.1263.

1-(1-Methyl-1,2,5,6-tetrahydropyridin-3-yl) Ethanol **1d**

Viscous oil, 88%. ^{1}H NMR (200 MHz, $CDCl_3$): 5.64–5.70 (m, 1H), 4.12–4.24 (m, 1H, CHO), 2.89 (s, 2H), 2.30 (t, $J = 5.0$ Hz, 2H), 2.35 (s, 3H, NMe), 2.16–2.53 (m, 2H), 1.25 (d, $J = 6.4$ Hz, 3H, Me). ^{13}C NMR (50 MHz, $CDCl_3$): 140.04 (=C), 118.35 (=CH), 69.47 (OCH), 52.83, 51.66, 45.42 (NMe), 25.21, 21.54. MS (EI, 70 eV): 141 $[M]^+$.

(1-Benzyl-1,2,5,6-tetrahedropyridin-4-yl)-methanol **1e**

Viscous oil, 90%. ^{1}H NMR (200 MHz, $CDCl_3$): 7.25–7.41 (m, 5H), 5.59–5.66 (m, 1H), 4.01 (s, 2H, OCH_2), 3.60 (s, 2H, NCH_2), 2.95–3.02 (m, 2H), 2.61 (t, $J = 5.8$ Hz, 2H), 2.36 (s (br), 1H, OH), 2.10–2.21 (m, 2H). ^{13}C

NMR (50 MHz, $CDCl_3$): 137.64, 136.41, 129.29 (2C), 128.15 (2C), 127.08, 119.44, 65.75, 62.64, 52.32, 49.53, 26.21. MS (EI, 70 eV): 203 $[M]^+$.

General Procedure for the Synthesis of 6

Compounds **6a**, **6b**, **6c**, **6d**, **6e** were prepared according to the reference (7). To a 100-mL, three-neck flask with a stirring bar, 0.5 g of 2-iodo-6-methoxyphenol (2 mmol), 0.58 g of PPh_3 (2.2 mmol), 0.24 g of 3-hydroxy pyridine (2.2 mmol), and 10 mL, of dry CH_2Cl_2 were added under argon. Then, a solution of DEAD (0.38 g, 2.2 mmol) in 5 mL of CH_2Cl_2 was added dropwise at room temperature. After the addition was completed, the mixture was stirred for an additional 8 h at the same temperature. The solvent was removed under reduced pressure, and the residue was chromatographied to afford **6a** in 58% yield.

General Procedure for the Synthesis of Aryloxylalkyl Piperidines 2a–f

To a 250-mL flask with a stirring bar, 1.34 g of **6c** (4.3 mmol), 1.54 mL of MeI (2.21 g, 12.9 mmol), and 50 mL of CH_2Cl_2 were added. The mixture was stirred at room temperature for 24 h until the disappearance of **6c** as shown by TLC. The solid was filtered and washed with dichloromethane. The product was dried, and the yield of the product **7d** was 85%.

Then, 0.45 g of sodium borohydride (12 mmol) was added portionwise to 1.15 g of **7d** (2.4 mmol) in 10 mL of MeOH at 0°C. The mixture continued to stir at 0°C for 1 h and then at room temperature for 2 h. The solvent was evaporated under the reduced pressure, 5 mL of water was added, and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatograph to afford 0.75 g of **2d** (77%).

Data

5-[(2-Iodo-6-methoxyphenoxy)methyl]-1-methyl-1,2,5,6-tetrahedropyridine **2a**

Viscous oil, 10%. ^{1}H NMR (200 MHz, $CDCl_3$): 7.35 (dd, $J = 7.7$, 1.8 Hz, 1H, ArH), 6.89 (dd, $J = 8.1$, 1.8 Hz, 1H, ArH), 6.81 (t, $J = 7.7$ Hz, 1H, ArH), 5.89–5.95 (m, 1H), 4.48 (s, 2H), 3.84 (s, 3H, OMe), 3.25 (s, 2H), 2.73 (t, $J = 7.5$ Hz, 2H), 2.55 (s, 3H, NMe), 2.35–2.43 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): 152.70, 147.70, 132.32, 130.54, 125.77, 124.04, 112.74, 92.70 (=C-I), 75.04 (OCH_2), 55.88, 55.33, 51.24, 45.39 (NMe), 25.29. MS

(EI, 70 eV): 359 $[M]^+$. HRMS-EI calculated for $C_{14}H_{18}INO$: 359.0382; found: 359.0376.

5-[(2-Iodophenoxy)methyl]-1-methyl-1,2,5,6-tetrahedropyridine **2b**

Viscous oil, 36%. ^1H NMR (200 MHz, $CDCl_3$): 7.69 (dd, $J = 7.8$, 1.6 Hz, 1H), 7.19 (td, $J = 8.9$, 1.6 Hz, 1H), 6.74 (dd, $J = 9.5$, 1.1 Hz, 1H), 6.62 (td, $J = 7.7$, 1.4 Hz, 1H), 5.80–5.87 (m, 1H), 4.40 (s, 2H), 2.98 (s, 2H), 2.46 (t, $J = 5.8$ Hz, 2H), 2.33 (s, 3H, NMe), 2.14–2.24 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): 157.09, 139.34, 131.86, 129.24, 123.35, 122.52, 112.37, 86.63 (=C-I), 71.55, 54.96, 51.57, 45.75 (NMe), 25.73. MS (EI, 70 eV): 329 $[M]^+$. HRMS-EI calculated for $C_{13}H_{16}INO$: 329.0277; found: 329.0272.

1-Benzyl-5-[(2-iodophenoxy)methyl]-1,2,5,6-tetrahedropyridine **2c**

Viscous oil, 41%. ^1H NMR (200 MHz, $CDCl_3$): 76 (dd, $J = 7.7$, 1.5 Hz, 1H), 7.22–7.41 (m, 6H), 6.79 (dd, $J = 8.2$, 1.3 Hz, 1H), 6.7 (td, $J = 7.4$, 7.7, 1.4 Hz, 1H), 5.90–5.95 (m, 1H), 4.44 (s, 2H), 3.66 (s, 2H), 3.13 (dd, $J = 6.0$, 2.0 Hz, 2H), 2.61 (t, $J = 5.7$ Hz, 2H), 2.20–2.28 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): 157.14, 139.34, 138.15, 131.99, 129.21 (2C), 128.22 (3C), 127.01, 123.68, 122.56, 112.41, 86.79 (=C-I), 71.64, 62.68, 53.20, 49.47, 25.69. MS (EI, 70 eV): 405 $[M]^+$. HRMS-EI calculated for $C_{19}H_{20}INO$: 405.0590; found: 405.0594.

Compound **8b**

Yield 24%. ^1H NMR (200 MHz, $CDCl_3$): 7.29–7.37 (m, 5H, ArH), 6.24 (dt, $J = 9.7$, 2.1 Hz, 1H), 5.77–5.87 (m, 1H), 4.87 (s, 1H), 4.78 (s, 1H), 3.64 (s, 2H), 3.23 (t, $J = 1.1$ Hz, 2H), 3.07–3.14 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): 140.37, 137.85, 129.18 (2C), 128.23 (2C), 127.82, 127.62, 127.12, 110.76 (=CH_2), 61.82, 55.86, 52.14. MS (EI, 70 eV): 185 $[M]^+$. HRMS-EI calculated for $C_{13}H_{15}N$: 185.1204; found: 185.1210.

1-Benzyl-4-[(2-iodophenoxy)methyl]-1,2,5,6-pyridine **2d**

Viscous oil, 77%. ^1H NMR (200 MHz, $CDCl_3$): 7.77 (dd, $J = 7.8$, 1.6 Hz, 1H), 7.23–7.38 (m, 6H, ArH), 6.82 (dd, $J = 8.3$, 1.3 Hz, 1H), 6.70 (td, $J = 7.5$, 1.4 Hz, 1H), 5.82–5.88 (m, 1H), 4.47 (s, broad, 2H), 3.62 (s, 2H), 3.02–3.08 (m, 2H), 2.66 (t, $J = 5.8$ Hz, 2H), 2.26–2.35 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): 157.19, 139.37, 138.17, 131.801, 129.32, 129.13 (2C), 128.20 (2C), 127.04, 122.87, 122.52, 112.44, 86.69 (=C-I), 72.17, 62.59, 52.40, 49.44, 26.53. MS (EI, 70 eV): 405 $[M]^+$. HRMS-EI calculated for $C_{19}H_{20}INO$: 405.0590; found: 405.0585.

5-[2-(2-Iodo-6-methoxyphenoxy)ethyl]-1-methyl-1,2,5,6-tetrahedropyridine **2e**

Viscous oil, 64%. ^{1}H NMR (200 MHz, $CDCl_3$): 7.34 (dd, $J = 7.7$, 1.6 Hz, 1H), 6.89 (dd, $J = 8.2$, 1.6 Hz, 1H), 6.78 (t, $J = 7.8$ Hz, 1H), 5.62–5.69 (m, 1H), 4.05 (t, $J = 7.0$ Hz, 2H), 3.85 (s, 3H, OMe), 3.14 (s, 2H), 2.66 (t, $J = 5.9$ Hz, 2H), 2.54 (t, $J = 7.0$ Hz, 2H), 2.48 (s, 3H, NMe), 2.23–2.34 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): 152.75, 148.05, 132.09, 130.51, 125.67, 120.64, 112.69, 92.94 (=C-I), 71.54, 57.06, 55.87 (OMe), 51.37, 45.25 (NMe), 35.78, 25.33. MS (EI, 70 eV): 373 $[M]^+$. HRMS-EI calculated for $C_{15}H_{20}INO_2$: 373.0539; found: 373.0546.

1-Benzyl-4-((2-iodo-6-methoxyphenoxy)methyl)-1,2,5,6-tetrahydropyridine **2f**

Viscous oil, 75%. ^{1}H NMR (200 MHz, $CDCl_3$): 7.25–7.41 (m, 6H, ArH), 6.88 (dd, $J = 8.2$, 7.8 Hz, 1H, ArH), 6.8 (t, $J = 7.8$ Hz, 1H, ArH), 5.80–5.88 (m, 1H), 4.39 (s, 2H), 3.83 (s, 3H, OMe), 3.62 (s, 2H), 2.99–3.10 (m, 2H), 2.67 (t, $J = 5.9$ Hz, 2H), 2.40–2.49 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): 152.89, 147.90, 138.42, 132.99, 130.66, 129.09 (2C), 128.16 (2C), 126.96, 125.73, 123.77, 112.80, 92.82 (=C-I), 75.84, 62.62, 55.92 (OMe), 52.57, 49.66, 22.17. MS (EI, 70 eV): 435.30 $[M]^+$. HRMS-EI calculated for $C_{20}H_{22}INO_2$: 435.0695; found: 435.0687.

ACKNOWLEDGMENT

We thank the EGIDE for financial support.

REFERENCES

1. (a) Pinder, A. R. Azetidine, pyrrole, pyrrolidine, piperidine, and pyridine alkaloids. *Nat. Prod. Rep.* **1992**, *9*, 491–504; (b) Dewick, P. M. *Medicinal Natural Products*; John Wiley and Sons: Chichester, 1997, Chapter 6; (c) Michael, J. P. Indolizidine and quinolizidine alkaloids. *Nat. Prod. Rep.* **2004**, *21*, 625–649; (d) O'Hagan, D. Pyrrole, pyrrolidine, pyridine, piperidine and tropane alkaloids. *Nat. Prod. Rep.* **2002**, *17*, 435–446; (e) Maison, W. In *Highlights in Bioorganic Chemistry*; Schmuck, C., Wennemers, H., Eds.; Wiley-VCH: New York, 2004, pp. 18–29; (f) Maier, C. A.; Wunsch, B. Novel σ receptor ligands. Part 2. SAR of spiro[[2]-benzopyran-1,4′-piperidines] and spiro[[2]benzofuran-1,4′-piperidines] with carbon substituents in position 3. *J. Med. Chem.* **2002**, *45*, 4923–4930; (g) Maier, C. A.; Wunsch, B. Novel spiropiperidines as highly potent and subtype selective σ-receptor ligands. Part 1. *J. Med. Chem.* **2002**, *45*, 438–448; (h) Zaveri, N. Peptide and nonpeptide ligands for the nociceptin/orphanin FQ

receptor ORL1: Research tools and potential therapeutic agents. *Life Sci.* **2003**, *73*, 663–678.

2. (a) Buffat, M. G. P. Synthesis of piperidines. *Tetrahedron* **2004**, *60*, 1701–1729; (b) Felpin, F. X.; Leberton, J. Synthesis of 2,6-dialkyl-1,2,5,6-tetrahydropyridines and their applications in total synthesis. *Curr. Org. Synth.* **2004**, *1*, 83–109; (c) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. Recent advances in the synthesis of piperidones and piperidines. *Tetrahedron* **2003**, *59*, 2953–2989; (d) Laschat, S.; Dickner, T. Stereoselective synthesis of piperidines. *Synthesis* **2000**, 1781–1813; (e) Rubiralata, M.; Giralt, E.; Diez, A. *Piperidine: Structure, Preparation, Reactivity, and Synthetic Applications of Piperidines and its Derivatives*; Elsevier: New York, 1991; (f) Zhou, X.-F.; Lan, J.; Kwon, O. An expedient phospohine-catalyzed [4 + 2] annulation: Synthesis of highly functionalized tetrahydropyridines. *J. Am. Chem. Soc.* **2003**, *125*, 4716–4717; (g) Wurz, R. P.; Fu, G. C. Catalytic asymmetric synthesis of piperidine derivatives through the [4 + 2] annulation of imines with allenes. *J. Am. Chem. Soc.* **2005**, *127*, 12234–12235.
3. (a) Sakagami, H.; Kamikubo, T.; Ogasawara, K. Novel reduction of 3-hydroxypyridine and its use in the enantioselective synthesis of (+)-pseudoconhydrine and (+)-N-methylpseudoconhydrine. *Chem. Commun.* **1996**, 1433–1434; (b) Sakagami, H.; Ogasawara, K. Lipase-mediated synthesis of enantiopure N-carbobenzoxy-3-hydroxy-1,2,3,4-tetrahydro- and N-carbobenzoxy-3-hydroxy-1,2,3,6-tetrahydropyridines from 3-hydroxypyridine. *Synthesis* **2000**, 521–524; (c) Tanaka, H.; Sakagami, H.; Ogasawara, K. Diastereoselective synthesis of 3,5-trans-(+)-(3R,5R)-3-carbomethoxycarbapenam from 3-hydroxypyridine: questioning the stereochemical assignment of the natural product. *Tetrahedron Lett.* **2002**, *43*, 93–96; (d) Cheng, C.-Y.; Hsin, L.-W.; Liou, J.-P. Novel radical synthesis of morphine fragments spiro[benzofuran-3(2H),4′-piperidine] and octahydro-1H-benzofuro[3,2-e]isoquinoline. *Tetrahedron* **1996**, *52*, 10935–10944; (e) Cheng, C.-Y.; Liou, J.-P.; Lee, M.-J. Synthesis of morphine fragments spiro[benzofuran-3(2H),4′-piperidine] and octahydro-1H-benzofuro[3,2-e]isoquinoline by intramolecular Heck reaction. *Tetrahedron Lett.* **1997**, *38*, 4571–4574.
4. (a) Lambrecht, G.; Moser, U.; Mutscher, E.; Walther, G.; Wess, J. Muscarinic ganglionic stimulants: conformationally restrained analoges related to [4-[[N-(3-chlorophenyl)carbamoyl]oxy]-2-butynyl] trimethylammonium chloride. *J. Med. Chem.* **1986**, *29*, 1309–1311; (b) Grierson, D. S.; Bettiol, J. L.; Buck, I.; Husson, H. P.; Rubiralta, M.; Diez, A. Synthesis of 20-deethylsilicine from a second-generation 2-cyano-, DELTA, 3-piperidine synthon. *J. Org. Chem.* **1992**, *57*, 6414–6421.
5. Longlois, Y.; Longlois, N.; Potier, P. Application d'un schema biogenetique en synthese totale: L'ellipticine. *Tetrahedron Lett.* **1975**, *16*, 955–958.
6. (a) Bosmans, J. R. M. A.; Love, C. J.; Decleyn, M. A. J.; D'haen, H. E. F. Esters of 3-hydroxy-piperidinemethanol derivatives. *PCT Int. Appl.* **1997**, WO9730031 A1 79970821; (b) Chang, M.; Chen, S.; Chang, N. An efficient synthesis of N-alkyl-4-substituted-3H-pyridine-2,6-dione. Synthesis of isoguvacine and MDL-11,939. *Heterocycles* **2002**, *57*, 2321–2334.
7. (a) Mitsunobu, O. The use of diethyl azodicarboxylate and triphenylphosphine in synthesis and transformation of natural products. *Synthesis* **1981**, 1–28; (b) Charette, A. B.; Janes, M. K.; Boezio, A. A. Mitsunobu reaction using triphenylphosphine linked to Non-cross-linked polystyrene. *J. Org. Chem.* **2001**, *66*, 2178–2180; (c) Bitter, I.; Csokai, V. An expedient route to

p-tert-butylthiacalix[4]arene 1,3-diethers via Mitsunobu reactions. *Tetrahedron Lett.* **2003**, *44*, 2261–2265.
8. (a) Person, D. E.; Wysong, R. D.; Breder, C. V. Ortho bromination of phenols. *J. Org. Chem.* **1967**, *32*, 2358–2360; (b) Marcot, B.; Mayrargue, J.; Moskowitz, H.; Ducrot, P.; Thal, C. New stereoselective synthesis of spirocyclohexanbenzopyran derivatives. *Heterocyclic Commun.* **1995**, *1*, 289–296.
9. Malan, P. L.; Dean, P. M. The pyridylthioacetmorpholides and pyridylacetic acids. *J. Am. Chem. Soc.* **1947**, *69*, 1797–1798.