Tetrahedron 66 (2010) 7399–7404

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Improved synthetic pathway for the derivatization of huprine scaffold

Cyril Ronco [a], Ludovic Jean [a], Pierre-Yves Renard [a,b,*]

[a] Equipe de Chimie Bio-Organique, CNRS UMR 6014-COBRA & FR 3038, IRCOF, rue Lucien Tesnière, 76131 Mont-Saint-Aignan Cedex, France
[b] Institut Universitaire de France, 103 boulevard Saint Michel,75005 Paris, France

ARTICLE INFO

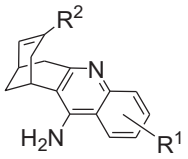
Article history:
Received 22 June 2010
Received in revised form 6 July 2010
Accepted 9 July 2010
Available online 16 July 2010

Keywords:
Huprine
Oxaadamantanol fragmentation
Friedländer condensation
Refortmasky reaction

ABSTRACT

In the search of new huprine-like acetylcholinesterase binders, we have developed an improved, shorter, and high-scalable synthetic pathway for the huprine synthesis based on a Reformatsky reaction–one-pot fragmentation/Friedländer condensation sequence. An extension for the one-pot synthesis of huprine-like 4-chloroquinolines is also presented. This modified route is particularly interesting as it allows to yield a huprine containing a functional group at position 9 in only three steps from commercially available material.

1. Introduction

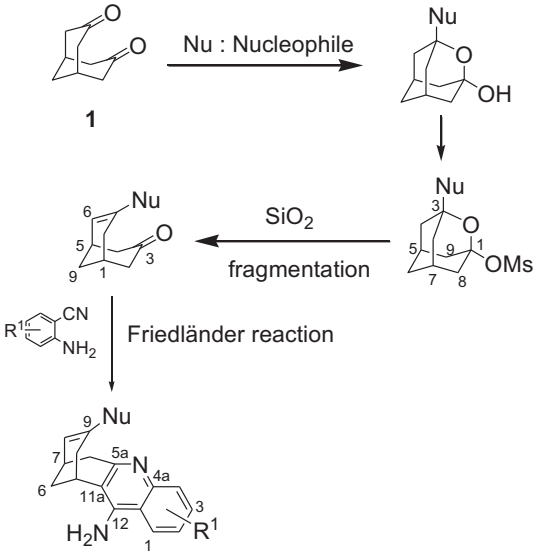


Scheme 1. General structure of Huprine.

Huprines are compounds of interest in relation with the symptomatic treatment of Alzheimer's disease cognitive disorders since they are very potent acetylcholinesterase (AChE) inhibitors.[1,2] In order to increase their anti-AChE activity, the selectivity for this enzyme or to prepare new heterodimers in view to obtain an additional action against amyloid peptide aggregation and deposit (via AChE peripheral site binding), new analogues with high binding affinities are desirable. Short and efficient synthetic pathways to afford these compounds would also be preferred (Scheme 1).

For these purposes, one of the most interesting modifications to explore within this structure is the functionalization at position 9, which could lead to a large number of derivatives. Indeed, only few variations at this position have been described, mostly due to synthetic difficulties.

The reported synthetic pathways for huprines begins with the addition of a nucleophile (organolithium, –magnesium or –cerium reagents) on bicyclo[3.3.1]nonane-3,7-dione **1** to afford an adamantanol-like structure (Scheme 2).[1b,3] Then the hydroxyl group of the hemiacetal is transformed into mesylate and the molecule submitted to silica gel-promoted fragmentation. The resulting bicyclo[3.3.1]non-6-en-3-ones are then engaged in a Friedländer condensation with the appropriate 2-aminobenzonitrile to afford the huprine core (Scheme 2).



Scheme 2. Synthetic pathway for huprines.

* Corresponding author. Tel.: +33 2 35 52 24 14; fax: +33 2 35 52 29 59; e-mail address: pierre-yves.renard@univ-rouen.fr (P.-Y. Renard).

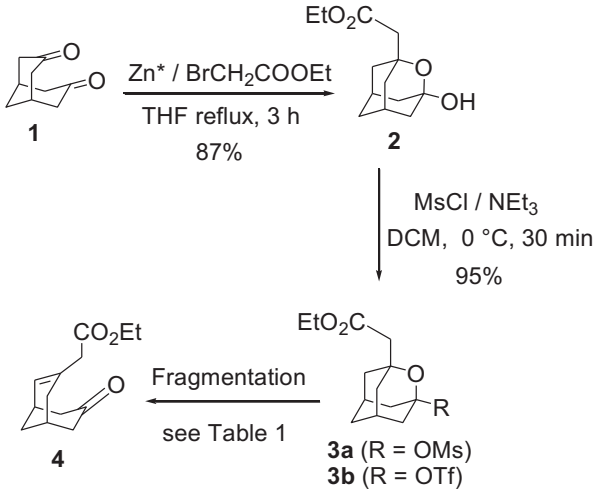
0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.07.021

In all the cases, the fragmentation step proved problematic and highly substituent-dependent. As a result, only huprines bearing short alkyl, alkenyl or phenyl groups have been described. Moreover, as illustrated by unsuccessful attempts described below, no molecule containing a functional group at this position has ever been synthesized.[3]

In this paper, we purpose a modified shorter and efficient synthetic pathway for huprines affording in three steps from commercial source a functionalizable huprine, parent compound of a potential wide range of derivatives.

2. Results and discussion

In order to graft a functional group at position 9 of the huprine, we choose to attach an ester group via a Reformatsky reaction (Scheme 3). This reaction was performed by addition of ethyl bromoacetate to the starting bicyclo[3.3.1]nonane-3,7-dione **1** in the presence of activated zinc dust. Using modified standard conditions,[4] both reaction partners were introduced in refluxing THF and afforded after 3 h the oxaadamantanol **2** in 87% yield.



Scheme 3. Tandem Reformatsky reaction—fragmentation sequence to afford 7-functionalized bicyclo[3.3.1]non-6-en-3-one **4**.

Taking into account the potential risk of side-reactions on this type of substrates, those yields are satisfactory and favorably comparable to those obtained with nucleophilic additions of organomagnesium, organolitium or organocerium reagents on bicyclo[3.3.1]nonane-3,7-dione **1**. The use of zinc reagents and Reformatsky reaction consists thus in an interesting alternative method to afford oxaadamantanols bearing a group with further functional modification ability. Furthermore, these results represent one of the rare examples of additions of Reformatsky reagents on dione **1**.[5]

The next step towards functionalized huprines is the ring fragmentation to get bicyclo[3.3.1]non-6-en-3-one **4** (Scheme 3). Thus, after mesylation of oxaadamantanol **2**, we focused our attention on the fragmentation of mesylate **3a** to validate suitable reaction conditions before any further functionalization of the ester (Table 1). Indeed this reaction proved more difficult than expected as no reaction happened under previously described reaction conditions using silica gel in dichloromethane (entry 1).[3] Increasing progressively the reaction time until four days (entry 2) or using a Brønsted acid failed (entry 3). We also explored the replacement of the mesylate by a triflate leaving group (**3b**) and to substitute the silica gel by an Amberlite resin gel (entries 4, 5, and 6), but all these attempts led to mixtures of starting compound in majority along with hydrolysis and degradation products in smaller amounts. Finally, by increasing reaction temperature, fragmentation product **4** could be obtained in low yield and generally in mixture with **3a** or/and **2** (entries 7–11), sometimes with additional degradation products. Surprisingly, the use of refluxing THF resulted only in hydrolyzed material probably due to a solvent effect (entry 9). Thus, we concluded from this study that the key factor would be to find a good compromise between acidity of the medium, reaction temperature, and reaction time.

After optimization of these conditions, this stable mesylate **3a** was treated by silica gel in refluxing 1,2-dichloroethane (DCE) for 18 h affording fragmentation product **4** in 38% yield and **2** in only 4% yield (entry 11).

Nevertheless, these results remained modest and not satisfactory in view of the establishment of an efficient method for the preparation of 9-functionalized huprine derivatives. The main problem is that silica gel-promoted fragmentation requires time and heat and that simultaneous hydrolysis of the mesylate occurs under these conditions.

With the goal in mind to have the same reactants and solvents than for the Freidländer reaction, aluminium trichloride was evaluated as the Lewis Acids. We found that aluminum trichloride was not only able to successfully fragment the oxaadamantanol, but also to drastically reduce the reaction time (from many hours to few minutes) and consequently increase the yield of the reaction without appearance of hydrolysis product (entry 12). By heating mesylate **3a** in the presence of a slight excess of anhydrous aluminum trichloride in refluxing 1,2-dichloroethane for just few minutes, the conversion into enone **4** proved total (100% conversion revealed by ^{1}H NMR after 10 min, 92% isolated yield). These reaction conditions are of higher interest, taking into account that

Table 1
Fragmentation attempts of oxaadamantanols **3a**,**b**

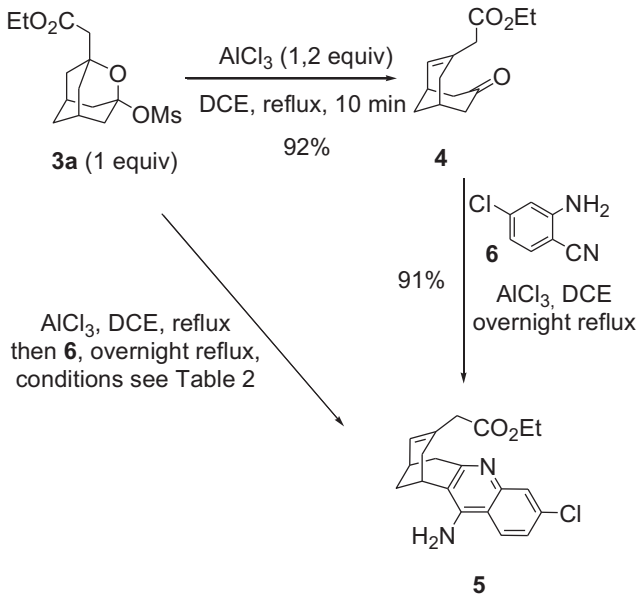
Entry	Reactant	Reagents	Solvent	Temperature	Time	Isolated yield (%)		
						Hydrolyzed product **2**	Starting material **3**	Fragmentation product **4**
1	**3a**	Silica gel	CH_2Cl_2	rt	13 h		78%	
2	**3a**	Silica gel	CH_2Cl_2	rt	96 h		76%	
3	**3a**	AcOH (4.5 equiv)	CH_2Cl_2	rt	15 h		98%	
4	**3b**	Silica gel	CH_2Cl_2	rt	90 h	33%	26%	
5	**3b**	Amberlite IR120	CH_2Cl_2	rt	90 h		95%	
6	**3a**	Amberlite IR120	CH_2Cl_2	rt	19 h		73%	
7	**3a**	Silica gel	CH_2Cl_2	Reflux	42 h	4%	5%	11%[a]
8	**3a**	Silica gel	CH_2Cl_2	Reflux	120 h	22%		33%[a]
9	**3a**	Silica gel	THF	Reflux	72 h	83%		
10	**3a**	Silica gel	$CHCl_3$	Reflux	40 h	33%		32%
11	**3a**	Silica gel	DCE	Reflux	18 h	4%		38%
12	**3a**	$AlCl_3$ (1.2 equiv)	DCE	Reflux	10 min			92%

[a] Significant amounts of degradation products.

silica gel-promoted fragmentations of oxaadamantanol mesylates displayed yields rarely upper than 50% in mixture with hydrolyzed material requiring further tricky separation.[1e,3] However, these conditions are especially convenient in the case of poorly reactive substrates such as **3a.**

In order to clarify the role of the mesylate leaving group in this reaction, we attempted the direct fragmentation of hemiacetal **2** in the same conditions. But the reaction failed, letting us come to conclusion to the necessity of the activation of the hydroxyl group.

The enone **4** was then condensed with 2-amino-4-chlorobenzonitrile **6** following a classical Friedländer procedure (aluminum trichloride, 1,2-dichloroethane reflux) to yield the desired functionalizable huprine **5** (91%). As expected, this reaction occurred with a preferential *anti* regioselectivity displaying *anti*/*syn* ratios of 100/0 to 96/4 (determined by ^{1}H NMR) depending on the assays (Scheme 4).



Scheme 4. Synthesis of huprine **5** from enone **4** or oxaadamantanol **3a**.

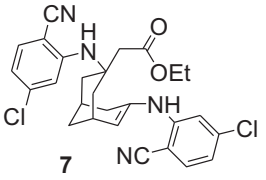
We have thenceforth developed an improved one-pot version of fragmentation and Friedländer condensation reactions using aluminum trichloride as Lewis acid (Table 2).

Table 2
One-pot fragmentation–Friedländer condensation attempts

Entry	$AlCl_3$ (equiv)	**6** (equiv)	Time[a] (min)	Yield (%)
1	2	2.1	[b]	35
2	3.5	1.75	[b]	45
3	1.5	1.1	[b]	48
4	3.5	1.75	5	49
5	1.2	1.05	0	57
6	3	1.1	5	70
7[c]	1.2	1.1	15	77
8	1.2	1.1	30	88
9[d]	2	1.1	0	85

[a] Reflux time before introduction of **6**.
[b] Compound **3a** was added to a mixture of **6** and $AlCl_3$.
[c] Reaction was carried out in a sealed tube at 90 °C.
[d] Reaction was refluxed in 1,1,2-trichloroethane.

The major side-product **7** of this reaction could be rationalized by the formation of enamine with a first equivalent of 2-amino-4-chlorobenzonitrile **6** followed by the attack of a second equivalent on the positive charged intermediate (Scheme 5). The formation of this side-product could have been minimized by using just 1.1 equiv of benzonitrile **6** and by introducing this latter after the fragmentation has occurred (Table 2, entries 6–8).

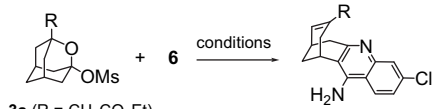


Scheme 5. Structure of isolated major side-product **7**.

Thus, by placing mesylate **3** and 1.2 equiv of aluminum trichloride in refluxing 1,2-dichloroethane, the fragmentation occurred within 10 min (checked by ^{1}H NMR). Then 1.1 equiv of 2-amino-4-chlorobenzonitrile **6** was introduced in the refluxing mixture to form immediately the Schiff base, which rearranges into enamine. The cyclization and aromatization requires further overnight heating at reflux temperature to afford the huprine core (Scheme 4). Additionally, this cascade reaction processed regioselectively with the same *anti*/*syn* ratios and displayed high optimized yield (88%) after silica-gel chromatography or recrystallisation. Increasing the temperature to 110 °C by using 1,1,2-trichloroethane as solvent did not improve the yield nor the ratio *anti*/*syn* (96/4) in favor of the *anti* regioisomer (Table 2, entry 9).

To generalize the method, we submitted other oxaadamantanols to this reaction pattern to afford the corresponding huprines (Table 3). Most described and active huprines **10** and **11** could thus be synthesized in better yields and one step less, confirming the improvement of our method with regard to silica gel promoted fragmentation.

Table 3
Comparison between silica gel pathway and $AlCl_3$ pathway for the preparation of huprines **5**, **10**, and **11**



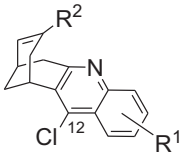
3a (R = CH_2CO_2Et)
8 (R = Me)
9 (R = Et)

5 (R = CH_2CO_2Et)
10 (R = Me)
11 (R = Et)

Entry	Reagent	Yield (%)[a]	
		SiO_2 conditions[b]	$AlCl_3$ conditions[d]
1	**3a**	35	88
2	**8**	29[c]	89
3	**9**	18[c]	85

[a] Overall yield from the corresponding mesylate.
[b] In two steps via the formation of the corresponding enone .
[c] Calculated from references **1c**,**d** and 3.
[d] One-pot procedure using 1.2 equiv of $AlCl_3$, at 82 °C overnight.

Encouraged by these results, we also tried to extend this one-pot version to the preparation of 4-chloroquinolines with the framework of huprine (Scheme 6), which are of great interest for the synthesis of huprine-based heterodimeric AChE inhibitors but present a problematic synthesis.

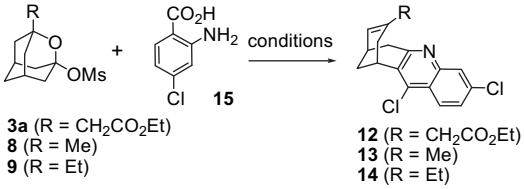


Scheme 6. General structure of huprine-like 4-chloroquinolines.

Indeed, based on the Carlier et al. methodology,[6] huprine-like 4-chloroquinolines are obtained in much lower yields than the corresponding tacrines. For this purpose, Camps et al. synthesized a 4-chloroquinoline in three steps from mesylate **9** and anthranilic acid in 18% overall yield.[7] More recently, we described the synthesis of 4-chloroquinolines **13** and **14**[2a] by performing a one pot condensation–chlorination reaction inspired from the Hu and Lu conditions.[8]

This preparation has been shortened by using aluminum trichloride promoted fragmentation (Table 4). As phosphorous oxychloride was found a too weak Lewis acid to fragment the oxaadamantanol structure of mesylate **3a**, the presence of both $AlCl_3$ (for fragmentation) and $POCl_3$ (for chlorination) was required.

Table 4
Comparison between silica gel pathway and $POCl_3/AlCl_3$ pathway for the preparation of 4-chloroquinolines **12**–**14**



3a (R = CH_2CO_2Et)
8 (R = Me)
9 (R = Et)

12 (R = CH_2CO_2Et)
13 (R = Me)
14 (R = Et)

Entry	Reagent	Yield[a] (%)	
		SiO_2 conditions[b]	$POCl_3/AlCl_3$ conditions[d]
1	**3a**	8	44
2	**8**	19[c]	40
3	**9**	18[c]	37

[a] Overall yield from the corresponding mesylate.
[b] In two steps via the formation of the corresponding enone.
[c] Calculated from references **1c**, **2**, and **3**.
[d] One-pot procedure using 1.2 equiv of $AlCl_3$, 20 equiv of $POCl_3$ at 90 °C overnight.

The presented yields remained modest but competitive taking into account that this pathway avoids one or two synthetic stages. This procedure is mostly helpful for the preparation of huprine **12**, as this substrate underwent extensive degradation under $POCl_3$ reflux.

3. Conclusion

We have developed a shorter and efficient alternative pathway for the synthesis of huprines by performing a one-pot Lewis acid mediated fragmentation–Friedländer condensation, with an extension for the synthesis of huprine-like 4-chloroquinolines. This pathway is particularly interesting in combination with a Reformatsky reaction, which contribution has allowed to install a functionalizable ester at position 9 of the huprine scaffold. This modification is worthy since the presented huprine analogue **5** could be the starting point of a novel class of derivatives modified at position 9 with potential pharmacological activity. Moreover, this synthetic pattern processes in three steps from commercial source, around 60% overall yield and has been validated in large scale (50 g of huprine **5**).

4. Experimental

4.1. General

Column chromatography purifications were performed on silica gel (40–63 μm) from SdS. Thin-layer chromatography (TLC) was carried out on Merck DC Kieselgel 60 F-254 aluminum sheets. Compounds were visualized by one of the two following methods: (1) illumination with a short wavelength UV lamp (λ=254 nm) or (2) staining with a 3.5% (w/v) phosphomolybdic acid solution in absolute ethanol. All solvents were dried following standard procedures (CH_2Cl_2 and 1,2-dichloroethane: distillation over P_2O_5, THF: distillation over Na/benzophenone).

Melting points were recorded on a LEICA VMHB Kofler system at atmospheric pressure and were uncorrected. Microanalyses were carried out on Carlo-Erba 1106. Infrared spectra were recorded as KBr pellets using a Perkin Elmer FT-IR Paragon 500 spectrometer with frequencies given in reciprocal centimeters (cm^{-1}). ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX 300 spectrometer (Bruker, Wissembourg, France). Chemical shifts are expressed in parts per million (ppm) from $CDCl_3$ (δ_H=7.26, δ_C=77.16), DMSO-d_6 (δ_H=2.50, δ_C=39.52) or CD_3OD (δ_H=3.31, δ_C=49.00).[9] *J* values are expressed in hertz. The ^1H and ^{13}C NMR spectra of all compounds were assigned through COSY $^1H/^1H$ and COSY $^1H/^{13}C$ spectra. The numbering of protons and carbon atoms has been established as indicated in Scheme 2. Mass spectra were obtained with a Finnigan LCQ Advantage MAX (ion trap) apparatus equipped with an electrospray source. All analyses were performed in the positive mode.

*4.1.1. Ethyl (3-hydroxy-2-oxatricyclo[3.3.1.1^{3,7}]dec-1-yl)acetate **2**.* To a suspension of activated zinc powder (oven-dried for at least 8 h and heated at the air gun under high vacuum just before use; 2.3 g, 35.0 mmol) in dry THF (50 mL) warmed to reflux temperature under argon, 1,2-dibromoethane (50 μL) was added dropwise through the condenser. After the effervescence has ceased a mixture of ethyl bromoacetate (1.5 mL, 12.5 mmol) and bicyclo[3.3.1]nonane-3,7-dione **1** (0.76 g, 5.00 mmol) in dry THF (100 mL) was added dropwise over 40 min. The green mixture was maintained at reflux temperature for 3 h (TLC monitoring), then cooled to rt and hydrolyzed by slow addition of saturated aqueous NH_4Cl solution (until pH=5–6). The resulting colorless solution with the zinc suspension was stirred for 10 min at rt before extraction with dichloromethane (3×60 mL). The combined organic layers were washed with saturated aqueous solution of $NaHCO_3$ (60 mL), then brine (60 mL), then water (60 mL), dried over $MgSO_4$, and concentrated under reduced pressure to afford an orange oil. Purification by flash chromatography (EtOAc/cyclohexane 4/6, v/v) afforded the desired oxaadamantanol **2** as white solid (1.04 g, 87%). R_f (EtOAc/cyclohexane 1/1, v/v)=0.40. Mp=74 °C. IR (KBr): ν=3433, 2928, 1732, 1066, 991 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=1.22 (t, *J*=7.2 Hz, 3H, H_{14}), 1.62–1.80 (m, 10H, H_4, H_6, H_8, H_9, H_{10}), 2.30–2.40 (m, 2H, H_5, H_7), 2.43 (s, 2H, H_{11}), 4.10 (q, *J*=7.2 Hz, 2H, H_{13}). ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.3 (C_{14}), 29.5 (C_5, C_7), 33.7 (C_6), 38.5 (C_4, C_{10}), 41.1 (C_8, C_9), 47.1 (C_{11}), 60.4 (C_{13}), 75.4 (C_3), 94.9 (C_1), 170.4 (C_{12}). MS (ESI^+): *m*/*z* (%): 258 (97) $[M+H_2O]^+$•, 241 (100) $[M+H]^+$. Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.05; H, 8.27.

*4.1.2. Ethyl {3-[(methylsulfonyl)oxy]-2-oxatricyclo[3.3.1.1^{3,7}]dec-1-yl}acetate **3a**.* A solution of oxaadamantanol **2** (600 mg, 2.50 mmol) and triethylamine (540 μL, 3.75 mmol) in dry dichloromethane (12 mL) under argon was cooled to 0 °C. Methane sulfonyl chloride (290 μL, 3.75 mmol) was then added dropwise and the cooling bath was allowed to melt. After 30 min stirring, the solution was carefully poured onto a saturated aqueous solution of $NaHCO_3$ (20 mL). The organic layer was separated and the aqueous one extracted with dichloromethane (3×20 mL). The combined organic layers were washed with brine (20 mL) then water (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure to afford an orange oil. This crude product was then filtered through a plug of silica gel and washed with EtOAc/cyclohexane 3/7, v/v mixture to afford the desired product as quite yellow oil (800 mg) pure enough to carry on the synthesis. Purification by flash chromatography (EtOAc/cyclohexane 2/8, v/v) afforded the desired mesylate **3a** as white crystals (755 mg, 95%). R_f (EtOAc/cyclohexane 1/1, v/v)=0.62. Mp=88 °C. IR (KBr): ν=2930, 1715, 1360, 1182, 1017 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=1.25 (t, *J*=7.2 Hz, 3H, H_{14}), 1.60–1.75 (m, 4H, H_4, H_{10}, H_6, H_6), 1.85–2.00 (m, 4H, H_4, H_{10}, H_8,

H_9), 2.15–2.30 (m, 2H, H_8, H_9), 2.40–2.45 (m, 2H, H_5, H_7), 2.49 (s, 2H, H_{11}), 3.17 (s, 3H, OMs), 4.13 (q, J=7.2 Hz, 2H, H_{13}). ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.2 (C_{14}), 29.8 (C_5, C_7), 33.3 (C_6), 38.2 (C_4, C_{10}), 39.5 (C_8, C_9), 42.0 (OMs), 46.5 (C_{11}), 60.5 (C_{13}), 77.9 (C_3), 107.4 (C_1), 169.7 (C_{12}). MS (ESI$^+$): m/z (%): 336 (100) $[M+H_2O]^{+\bullet}$, 319 (16) $[M+H]^+$, 223 (34) $[M-CH_3SO_3]^+$.

4.1.3. (±)-Ethyl (7-oxobicyclo[3.3.1]non-2-en-3-yl)acetate ***4***. To a suspension of anhydrous aluminum trichloride (720 mg, 5.40 mmol) in dry 1,2-dichloroethane (12 mL) under argon was added a solution of mesylate **3a** (1.43 g, 4.50 mmol) by portions. The mixture was heated to reflux and maintained at this temperature for 30 min then cooled to rt. The dark limpid solution was slowly diluted with water (24 mL) and THF (24 mL), basified by addition of aqueous 5 M NaOH (10 mL) and stirred at rt 10 min before extraction with dichloromethane (2×50 mL), then with EtOAc (2×50 mL). The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure to afford pale yellow oil. Purification by flash chromatography (EtOAc/cyclohexane 0/10 to 3/7, v/v) afforded the desired bicyclo[3.3.1]non-6-en-3-one **4** as colorless oil (920 mg, 92%). R_f (EtOAc/cyclohexane 1/1, v/v)=0.75. IR (thin film): ν=2932, 1732, 1414, 1368, 1336, 1257, 1177, 1032. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.11 (t, J=7.1 Hz, 3H, H_{13}), 1.70–1.90 (m, 3H, H_{8endo}, H_9), 2.10–2.25 (m, 2H, H_{2endo}, H_{4endo}), 2.25–2.40 (m, 3H, H_{8exo}, H_{4exo}, H_{2exo}), 2.45–2.55 (m, 1H, H_1), 2.55–2.65 (m, 1H, H_5), 2.75 (s, 2H, H_{10}), 3.97 (q, J=7.1 Hz, 2H, H_{12}), 5.47 (d, J=5.6 Hz, 1H, H_6). ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.9 (C_{13}), 29.6 (2C, C_1, C_9), 30.9 (C_5), 35.6 (C_8), 42.6 (C_{10}), 45.9 (C_4), 48.6 (C_2), 60.3 (C_{12}), 128.8 (C_6), 130.0 (C_7), 171.0 (C_{11}), 211.1 (C_3). MS (ESI$^+$): m/z (%): 223 (100) $[M+H]^+$. Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.45; H, 8.29.

4.1.4. (±)-Ethyl (12-amino-3-chloro-6,7,10,11-tetrahydro-7,11-methanocycloocta[b]quinolin-9-yl)acetate ***5***. *Procedure for preparation from enone* **4**. To a suspension of anhydrous $AlCl_3$ (980 mg, 7.35 mmol) and 2-amino-4-chlorobenzonitrile **6** (1.10 g, 7.35 mmol) in dry 1,2-dichloroethane (10 mL) under argon was added a solution of enone **4** (1.09 g, 4.90 mmol) in dry 1,2-dichloroethane (10 mL) dropwise over 10 min at rt. The reaction mixture was stirred at reflux for 14 h then cooled to rt. The solution was diluted with water (25 mL) and THF (25 mL), basified by addition of aqueous 5 M NaOH solution (30 mL) and stirred at rt for 30 min. The solution was then extracted with dichloromethane (2×50 mL) then with EtOAc (3×50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to afford a yellow solid. Purification by flash chromatography (cyclohexane/EtOAc 1/1 to EtOAc/MeOH 95/5, v/v) or by recrystallisation from diisopropyl ether/petroleum ether mixtures afforded the desired huprine ***5*** as a white solid (1.60 g, 91%). R_f (EtOAc/MeOH 9/1, v/v)=0.33. Mp=179–180 °C. IR (KBr): ν=3352, 3209, 2929, 1727, 1648, 1609,1559, 1490, 1426, 1371, 1308, 1285, 1258, 1154, 1031, 929 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.02 (t, J=7.2 Hz, 3H, H_{17}), 1.96 (br d, 1H, $J\approx$12 Hz, H_{10}), 2.02–2.15 (m, 2H, H_{10}, H_{13}), 2.60 (dd, J=17.1, 3.9 Hz, 1H, H_{13}), 2.70–2.74 (m, 1H, H_7), 2.72–2.77 (m, 2H, H_{14}), 2.97 (d, J=17.7 Hz, 1H, H_6), 3.15 (dd, J=17.5, 5.5 Hz, 1H, H_6), 3.20–3.28 (m, 1H, H_{11}), 3.95 (q, J=7.1 Hz, 2H, H_{16}), 4.71 (brs, 2H, NH_2), 5.72 (d, J=5.1 Hz, 1H, H_8), 7.30 (dd, J=9.0, 1.9 Hz, 1H, H_2), 7.62 (d, J=9.0 Hz, 1H, H_1), 7.85 (d, J=1.9 Hz, 1H, H_4). ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.0 (C_{17}), 27.4 (C_{11}), 28.4 (C_7), 28.8 (C_{10}), 33.9 (C_{13}), 39.2 (C_6), 43.3 (C_{14}), 60.6 (C_{16}), 114.9 (C_{11a} or C_{12a}), 115.8 (C_{11a} or C_{12a}), 121.9 (C_1), 124.7 (C_2), 127.1 (C_4), 129.5 (C_8), 129.8 (C_9), 134.6 (C_3), 146.4 (C_{4a} or C_{12}), 146.9 (C_{4a} or C_{12}), 158.1 (C_{5a}), 171.5 (C_{15}). MS (ESI$^+$): m/z (%): 359 (36), 357 (100) $[M+H]^+$. Anal. Calcd for $C_{20}H_{21}ClN_2O_2$: C, 67.32; H, 5.93; N, 7.85. Found: C, 67.36; H, 5.95; N, 8.02.

4.1.5. (±)-Ethyl (12-amino-3-chloro-6,7,10,11-tetrahydro-7,11-methanocycloocta[b]quinolin-9-yl)acetate ***5***. *Procedure for the one-pot fragmentation–Friedländer condensation from mesylate* **3a**. A suspension of anhydrous $AlCl_3$ (417 mg, 3.13 mmol) and mesylate **3a** (830 mg, 2.60 mmol) in dry 1,2-dichloroethane (4 mL) was heated to reflux temperature and the reflux was maintained for 30 min. The reaction mixture became orange and exothermic. Then, a suspension of 2-amino-4-chlorobenzonitrile **6** (438 mg, 2.87 mmol) in dry 1,2-dichloroethane (8 mL) was added dropwise to the refluxing mixture and the reflux was continued overnight (7-8 h are in most of the cases enough). The reaction mixture was then cooled to rt, diluted with water (10 mL) and THF (10 mL), basified by addition of aqueous 5 M NaOH solution (10 mL) and stirred at rt for 10 min. The phases were separated (dichloromethane was added if necessary) and the aqueous layer was extracted with EtOAc (3×20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to afford a yellow solid. Purification by flash chromatography (cyclohexane/EtOAc 1/1 to EtOAc/MeOH 95/5, v/v) or by recrystallisation from diisopropyl ether/petroleum ether mixtures afforded the desired huprine **5** as a white solid (817 mg, 88%).

4.1.6. (±)-12-Amino-3-chloro-9-methyl-6,7,10,11-tetrahydro-7,11-methanocycloocta[b]quinoline ***10***. *Procedure for the one-pot fragmentation–Friedländer condensation from mesylate* **8**. The procedure described above for huprine **5** was followed using mesylate **8** (246 mg, 1.00 mmol), $AlCl_3$ (160 mg, 1.20 mmol) and 2-amino-4-chlorobenzonitrile **6** (168 mg, 1.10 mmol). The reflux was maintained for 5 min before introduction of benzonitrile **6**. Purification by flash chromatography (cyclohexane/EtOAc 1/1 to EtOAc/MeOH 95/5, v/v) afforded the desired huprine **10** as a white solid (253 mg, 89%). ^{1}H and ^{13}C NMR data were in agreement with those given in the literature.[1,2a]

4.1.7. (±)-12-Amino-3-chloro-9-ethyl-6,7,10,11-tetrahydro-7,11-methanocycloocta[b]quinoline ***11***. *Procedure for the one-pot fragmentation–Friedländer condensation from mesylate* **9**. The procedure described above for huprine **5** was followed using mesylate **9** (260 mg, 1.00 mmol), $AlCl_3$ (160 mg, 1.20 mmol), and 2-amino-4-chlorobenzonitrile **6** (168 mg, 1.10 mmol). The reflux was maintained for 5 min before introduction of benzonitrile **6**. Purification by flash chromatography (cyclohexane/EtOAc 1/1 to EtOAc/MeOH 95/5, v/v) afforded the desired huprine **11** as a white solid (254 mg, 85%). ^{1}H and ^{13}C NMR data were in agreement with those given in the literature.[1,2a]

4.1.8. (±)-Ethyl(3,12-dichloro-6,7,10,11-tetrahydro-7,11-methano cycloocta[b]quinolin-9-yl)acetate ***12***. *Procedure for the one-pot fragmentation–Friedländer condensation from mesylate* **3a**. A mixture of **3a** (318 mg, 1.00 mmol), anhydrous aluminum trichloride (160 mg, 1.20 mmol), and 4 Å molecular sieves (~500 mg) in distilled 1,2-dichloroethane (3 mL) was stirred at reflux temperature for 30 min, then cooled to 30 °C. To the reaction mixture was added slowly a solution of 2-amino-4-chlorobenzoic acid **15** (206 mg, 1.20 mmol) in 1,4-dioxane (5 mL). The white precipitate, which formed was stirred at rt for 10 min then the mixture was cooled to 0 °C and phosphorous oxychloride (1.9 mL) was added dropwise. The reaction mixture was stirred at rt for 10 min then at 90 °C overnight, then hydrolyzed at 0 °C by slow addition of water (5 mL), THF (5 mL), and aqueous 5 M NaOH solution (12 mL). After 30 min stirring at rt, the salts were filtered and the residue washed with dichloromethane. The filtrate was extracted with dichloromethane (3×30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to afford a yellow oil. Purification by flash chromatography (cyclohexane/EtOAc 10/0 to 8/2, v/v) afforded the desired product **12** as a pale yellow solid (165 mg, 44%). R_f (cyclohexane/EtOAc 7/3, v/v)=0.59. IR (KBr): ν=2930, 1734, 1608,1545, 1474, 1396, 1369, 1332, 1294, 1253, 1153, 1074, 1033, 929, 770 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.96 (t, J=7.1 Hz, 3H, H_{17}), 1.92–1.99 (m, 1H, H_{10}), 2.07–2.14 (m, 1H, H_{10}), 2.19 (d, J=17.7 Hz, 1H,

H_{13}), 2.66 (dd, J=17.7, 5.5 Hz, 1H, H_{13}), 2.74–2.88 (m, 2H, H_7, H_{14}), 3.09 (dt, J=17.7, 1.9 Hz, 1H, H_6), 3.20 (dd, J=17.9, 5.3 Hz, 1H, H_6), 3.74–3.78 (m, 1H, H_{11}), 3.85–4.00 (m, H_{16}), 5.69 (d, J=5.5 Hz, 1H, H_8), 7.44 (dd, J=9.0, 1.9 Hz, 1H, H_2), 7.94 (d, J=1.9 Hz, 1H, H_4), 8.07 (d, J=9.0 Hz, 1H, H_1). ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.0 (C_{17}), 28.4 (C_{10}), 28.5 (C_7), 30.6 (C_{11}), 35.5 (C_{13}), 40.2 (C_6), 43.2 (C_{14}), 60.6 (C_{16}), 124.1 (C_{11a} or C_{12a}), 125.5 (C_1), 127.5 (C_2), 127.6 (C_4), 129.2 (C_8), 130.3 (C_{11a} or C_{12a}), 133.2 (C_9), 135.4 (C_3), 141.0 (C_{4a} or C_{12}), 147.5 (C_{4a} or C_{12}), 159.9 (C_{5a}), 171.3 (C_{15}). MS (ESI$^+$): m/z (%): 379 (15), 378 (67), 376 (100) $[M+H]^+$. Anal. Calcd for $C_{20}H_{19}Cl_2NO_2$: C, 63.84; H, 5.09; N, 3.72. Found: C, 62.33; H, 4.95; N, 3.71.

*4.1.9. (±)-3,12-Dichloro-9-methyl-6,7,10,11-tetrahydro-7,11-ethanocycloocta[b]quinoline **13**. Procedure for the one-pot fragmentation–Friedländer condensation from mesylate* **8**. The procedure described above for 12-chloroquinoline **12** was followed using mesylate **8** (260 mg, 1.00 mmol), $AlCl_3$ (160 mg, 1.20 mmol), and 2-amino-4-chlorobenzoic acid **15** (206 mg, 1.20 mmol). The reflux was maintained for 5 min before introduction of benzoic acid. Purification by flash chromatography (cyclohexane/EtOAc 10/0 to 8.5/1.5, v/v) afforded the desired product **13** as a white solid (122 mg, 40%). ^{1}H and ^{13}C NMR data were in agreement with those given in the literature.[2a]

*4.1.10. (±)-3,12-Dichloro-9-ethyl-6,7,10,11-tetrahydro-7,11-ethanocycloocta[b]quinoline **14**. Procedure for the one-pot fragmentation–Friedländer condensation from mesylate* **9**. The procedure described above 12-chloroquinoline **12** was followed using mesylate **9** (260 mg, 1.00 mmol), $AlCl_3$ (160 mg, 1.20 mmol), and 2-amino-4-chlorobenzoic acid **15** (206 mg, 1.20 mmol). The reflux was maintained for 5 min before introduction of benzoic acid. Purification by flash chromatography (cyclohexane/EtOAc 1/1 to EtOAc/MeOH 95/5, v/v) afforded the desired product **14** as a white solid (118 mg, 37%). ^{1}H and ^{13}C NMR data were in agreement with those given in the literature.[2a]

Acknowledgements

The french MRES ('Ministère de l'Enseignement Supérieur et de la Recherche') is acknowledged for Ph.D. Fellowship to C.R. FRM ('Fondation pour la Recherche Médicale'), IUF ('Institut Universitaire de France') the Région Haute Normandie (Crunch programm), and Agence Nationale pour la Recherche (ANR—detoxneuro BLAN06-1_134538) are gratefully acknowledged for their financial support. We also gratefully thank Dr. Anthony Romieu (Université de Rouen) for mass spectrometry measurements, Elisabeth Roger (INSA de Rouen) for IR measurements and Annick Leboisselier (INSA de Rouen) for the determination of elemental analyses.

Supplementary data

Synthetic procedure and analyses of compound **3b** and analyses of compound **7** including ^{1}H/^{13}C NMR assignments are detailed in supplementary data. ^{1}H and ^{13}C NMR spectra of all new compounds (**2**, **3a**, **4**, **5**, and **12**) are also included. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.07.021. These data include MOL files and InChIKeys of the most important compounds described in this article.

References and notes

1. (a) Muñoz-Torrero, D.; Camps, P. *Expert Opin. Drug Discovery* **2008**, *3*, 65–81; (b) Camps, P.; Muñoz-Torrero, D. *Mini-Rev. Med. Chem.* **2001**, *1*, 163–174; (c) Camps, P.; El Achab, R.; Morral, J.; Muñoz-Torrero, D.; Badia, A.; Baños, J. E.; Vivas, N. M.; Barril, X.; Orozco, M.; Luque, F. J. *J. Med. Chem.* **2000**, *43*, 4657–4666; (d) Camps, P.; Cusack, B.; Mallender, W. D.; El Achab, R.; Morral, J.; Muñoz-Torrero, D.; Rosenberry, T. L. *Mol. Pharmacol.* **2000**, *57*, 409–417; (e) Camps, P.; El Achab, R.; Görbig, D. M.; Morral, J.; Muñoz-Torrero, D.; Badia, A.; Baños, J. E.; Vivas, N. M.; Barril, X.; Orozco, M.; Luque, F. J. *J. Med. Chem.* **1999**, *42*, 3227–3242.
2. (a) Ronco, C.; Sorin, G.; Nachon, F.; Foucault, R.; Jean, L.; Romieu, A.; Renard, P.-Y. *Bioorg. Med. Chem.* **2009**, *17*, 4523–4536; (b) Ronco, C.; Renard, P.-Y.; Jean, L.; Nachon, F.; Romieu, A. EP10305366.6.
3. Camps, P.; El Achab, R.; Font-Bardia, M.; Görbig, D.; Morral, J.; Muñoz-Torrero, D.; Solans, X.; Simon, M. *Tetrahedron* **1996**, *52*, 5867–5880.
4. Cuenca, A. B.; D'Hooge, F.; Gouge, V.; Castelot-Deliencourt, G.; Oulyadi, H.; Leclerc, E.; Jubault, P.; Pannecoucke, X.; Quirion, J.-C. *Synlett* **2005**, 2627–2630 and references cited herein.
5. (a) Ross, N. A.; Bartsch, R. A.; Marchand, A. P. *ARKIVOC* **2003**, 27–30; (b) Marchand, A. P.; Wu, A. *J. Org. Chem.* **1986**, *51*, 1897–1900.
6. Carlier, P. R.; Han, Y. F.; Chow, E. S.-H.; Li, C. P.-L.; Wang, H.; Lieu, T. X.; Wong, H. S.; Pang, Y.-P. *Bioorg. Med. Chem.* **1999**, *7*, 351–357.
7. Camps, P.; Formosa, X.; Muñoz-Torrero, D.; Petrignet, J.; Badia, A.; Clos, M. V. *J. Med. Chem.* **2005**, *48*, 1701–1704.
8. Hu, M.-K.; Lu, C.-F. *Tetrahedron Lett.* **2000**, *41*, 1815–1818.
9. Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *J. Org. Chem.* **1997**, *62*, 7512–7515.