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Synthesis of diastereomeric 13-amido-substituted huprines as potential high affinity acetylcholinesterase inhibitors

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Abstract—Two diastereomeric huprines additionally functionalized at position 13 with a methanesulfonamido group have been synthesized in seven steps from the known 9,9-ethylenedioxybicyclo[3.3.1]nonane-3,7-dione (**5**). In a key-step, nickel boride non-stereoselective reduction of an oxime gave a mixture of amines which was separated as methanesulfonamido derivatives. The substitution pattern of these huprines could lead to an extended binding near the active site of acetylcholinesterase (AChE), and consequently to improved AChE inhibitors.

1. Introduction

Huprines, **1** (Fig. 1), have recently emerged as a new class of very potent and selective acetylcholinesterase (AChE) inhibitors of potential interest for the treatment of Alzheimer's disease, which have shown to be superior in terms of potency, selectivity and affinity to the most representative drugs among the very few ones approved to date for the symptomatic treatment of this disease.[1–4] Huprines were designed through a conjunctive approach from two of these representative AChE inhibitors, (−)-huperzine A, **2**, and tacrine, **3** (Fig. 1), by combining the carbobicyclic moiety of the first one with the 4-aminoquinoline subunit of the second one.[5,6] This design resulted in an extended binding of huprines in the active site of the enzyme as compared with the models from which they were designed, since they are able to interact simultaneously with several of the binding sites for tacrine and (−)-huperzine A, which are close and partially overlap within AChE. Consequently, these compounds displayed a higher affinity for AChE than **2** and **3**.

By the moment, the most powerful huprines are the so-called huprine X and huprine Y ((−)-**1**, R=Et and Me, respectively; R^1=H; R^3=Cl, Fig. 1).

Huprine X exhibits one of the highest affinities reported for a reversible inhibitor, being ca. 1200-fold higher than that of tacrine, 180-fold higher than that of (−)-huperzine A, and 40-fold higher than that of donepezil.[7] Molecular modeling studies,[1–3,8] recently validated by 3D X-ray diffraction analysis of a complex *Tc*AChE–huprine X,[9] have shown that: (a) the aromatic portion of huprine X occupies the same binding site as tacrine; (b) the chlorine substituent lies in a hydrophobic pocket, establishing additional interactions with other residues of the enzyme; and (c) the carbobicyclic unit of huprine X occupies the same binding pocket as the corresponding subunit of (−)-huperzine A. While huprines share essentially all of the features that modulate the interaction of tacrine with AChE, they share with (−)-huperzine A only the interactions due to the unsaturated

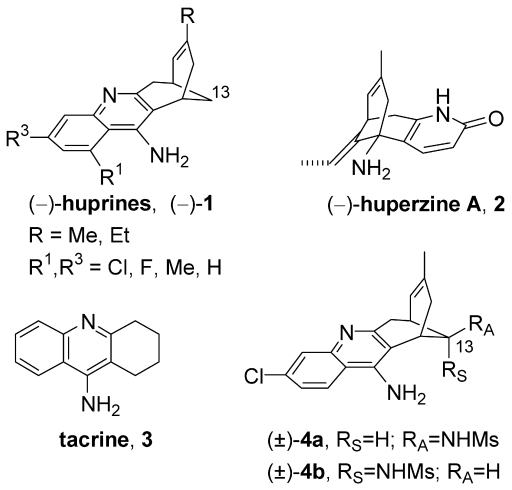

Figure 1. Structure of (−)-huprines, (−)-huperzine A, tacrine and novel 13-methanesulfonamido-substituted huprines.

Keywords: acetylcholinesterase inhibitors; methanesulfonamido derivatives; huprines.

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three-carbon bridge, since the heterocyclic portion of (−)-huprines (the most active enantiomers of huprines) and that of (−)-huperzine A point to opposite directions. Consequently, none of the hitherto synthesized huprines **1** is able to establish with AChE the important interactions due to the pyridone ring of (−)-huperzine A. From these results, it became apparent that the introduction of an amido functionality at the methylene bridge (position 13) of huprines could lead to novel compounds able to establish additional interactions with the active site of AChE, what must lead to an even more extended binding and to a still higher affinity for AChE.

In this paper, we describe the synthesis of the first two examples of such novel huprines in racemic form ((±)-**4a** and (±)-**4b**, Fig. 1), bearing the structural features of the most active huprines prepared to date, and an additional methanesulfonamido functionality at position 13 with the two possible configurations.

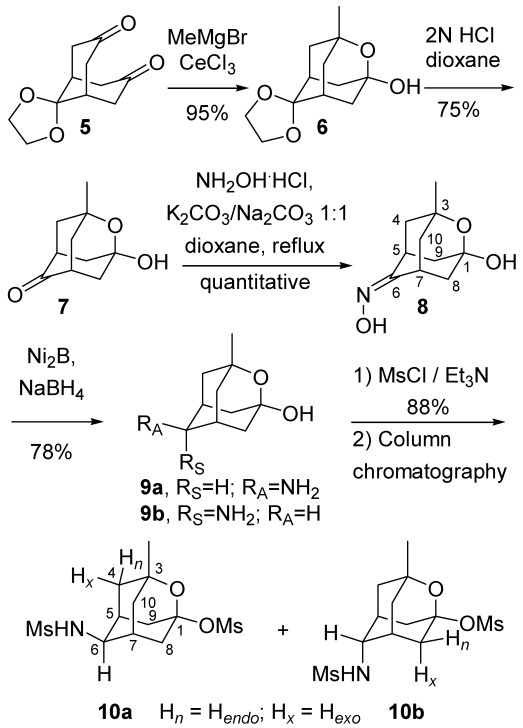
2. Results and discussion

Huprines **1** have been typically synthesized from bicyclo[3.3.1]nonane-3,7-dione through a sequence which involves, nucleophilic addition of a suitable organometallic reagent, mesylation of the resulting 3-alkyl-2-oxa-1-adamantanol, silica-gel induced fragmentation of the formed mesylate, and Friedländer condensation of the resulting 7-alkylbicyclo[3.3.1]non-6-en-3-one with a conveniently substituted 2-aminobenzonitrile.[1–7,10]

The synthesis of the novel huprines **4** was envisaged through a sequence similar to that described above, starting from the known[11] diketone **5** which, apart from the required keto functions, contains an ethylenedioxy group at the methylene bridge, from which the amido group would be generated (Scheme 1).

Reaction of **5** with $MeCeCl_2$ (prepared in situ from MeMgBr and $CeCl_3$) from −78°C to room temperature afforded in excellent yield the oxaadamantanol **6**, whose acetal group was efficiently hydrolyzed on reaction with 2N HCl in dioxane under reflux, giving rise to the known[10] ketone **7** in 75% yield. Reaction of **7** with $NH_2OH{\cdot}HCl$ in refluxing dioxane in the presence of a mixture of sodium and potassium carbonates afforded oxime **8** quantitatively.

Treatment of oxime **8** with a combination of nickel boride and $NaBH_4$ led to a mixture of diastereomeric amines **9** (78% yield) in an approximate ratio **9a/9b** of 1.1:1, which could not be separated by column chromatography. Differentiation of **9a** and **9b** was carried out by comparison of their ^{13}C NMR data with those of their derivatives **10a** and **10b**, respectively, whose configurations were unequivocally assigned (vide infra). Reaction of the diastereomeric mixture of amines **9** with an excess of MsCl and Et_3N in CH_2Cl_2 at −10°C afforded a mixture of diastereomeric sulfonamido mesylates **10a** and **10b** in 88% global yield. In sharp contrast with the chemical behavior of all of the oxaadamantyl mesylates hitherto prepared in our group, which easily fragmentate in the presence of silica gel at room temperature,[10] **10a** and **10b** turned out to be highly



Scheme 1. Obtention of diastereopure methanosulfonamido mesylates **10a** and **10b** from diketone **5**.

stable under these conditions, what allowed their chromatographic separation. Thus, column chromatography of the crude reaction product through silica gel, followed by recrystallization from AcOEt of the enriched chromatographic fractions afforded significant amounts of diastereopure **10a** and **10b**. The observation of a cross-peak in the COSY $^1H-^1H$ spectrum of **10a** between the signals of 6-H (δ 3.63 ppm) and 4(10)-H_{endo} (δ 1.63 ppm) corresponding to a long-distance W-coupling between these protons, was indicative of an *anti* arrangement of the methanesulfonamido and methanesulfonyloxy groups of **10a**. Similarly, a cross-peak in the COSY $^1H-^1H$ spectrum of **10b** between the signals of 6-H (δ 3.61 ppm) and 8(9)-H_{endo} (δ 2.15 ppm) was indicative of a *syn* arrangement of the methanesulfonamido and methanesulfonyloxy groups of **10b**. Worthy of note, the configurations assigned to **10a** and **10b** on the basis of their spectroscopic data were later confirmed by X-ray diffraction analysis of monocrystals of both compounds. Figures 2 and 3 show the ORTEP representation of compounds **10a** and **10b**, respectively.

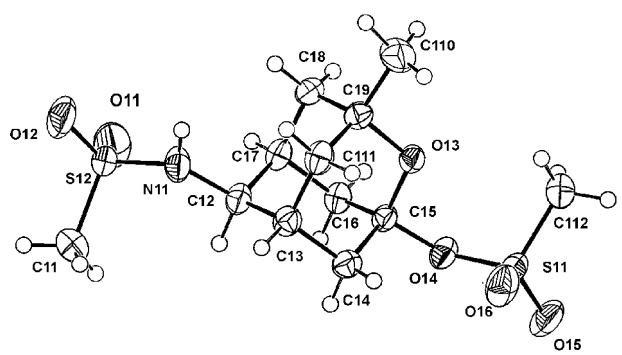


Figure 2. X-Ray diffraction structure (ORTEP) of compound **10a**.

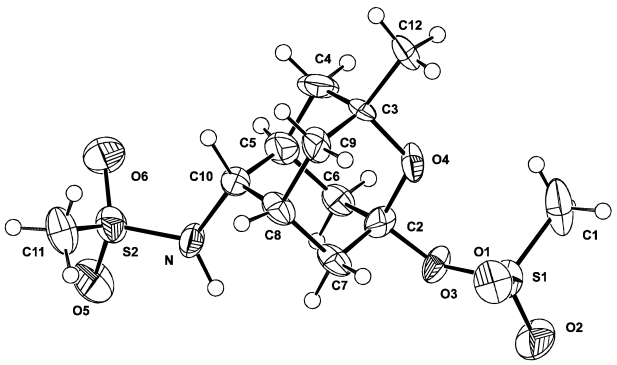
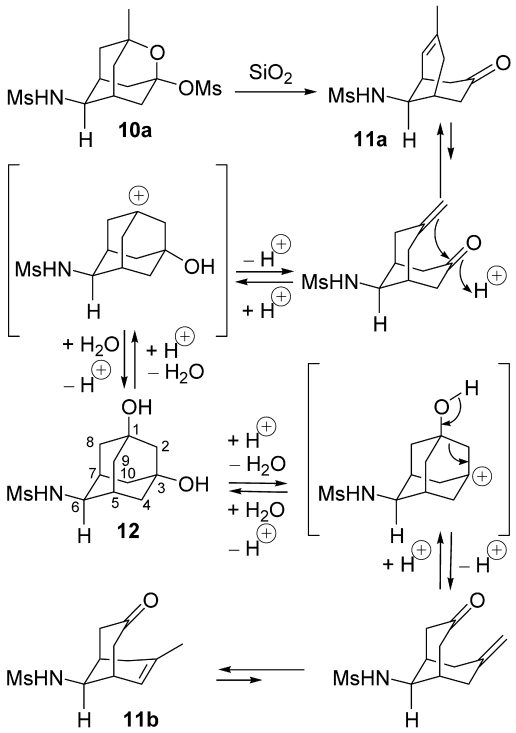


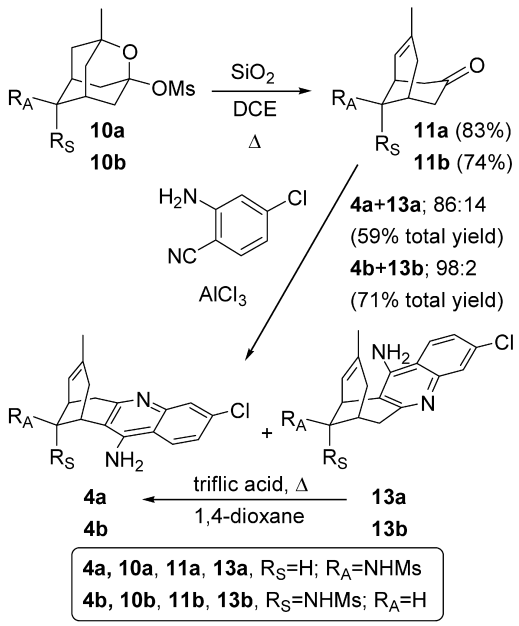
Figure 3. X-Ray diffraction structure (ORTEP) of compound **10b**.

Fragmentation of mesylates **10a** and **10b** required more forcing conditions than usual.[10] The best conditions imply the reaction of mesylate **10a** with silica gel in 1,2-dichloroethane (DCE) under reflux for 35 min that afforded the desired enone **11a** in 83% yield (Schemes 2 and 3).

Worthy of note, when the above reaction from diastereopure **10a** was carried out in refluxing 1,2-dibromoethane for 45 min, significant amounts of adamantanediol **12** (10–26% yield) and enone **11b** (1–3% yield) were isolated, after column chromatography of the crude product, in addition to the expected enone **11a** (38–56% yield) (Scheme 2). The formation of **12** could arise from an acid-catalyzed isomerization of the endocyclic carbon–carbon double bond of the initially formed fragmentation product **11a** to a less favored exocyclic position under the relatively forcing reaction conditions, followed by electrophilic addition of the activated carbonyl group to give a bridgehead adamantyl carbocation, which on reaction with water would give the 1,3-adamantanediol **12**. Moreover, under these reaction



Scheme 2. Possible mechanistic pathway for the formation of adamantanediol **12** and enone **11b** from diastereopure mesylate **10a**.



Scheme 3. Synthesis of the novel 13-methanosulfonamido-substituted huprines **4a** and **4b** from diastereopure mesylates **10a** and **10b**.

conditions, adamantanediol **12** could fragmentate to give a bicyclic enone bearing an exocyclic carbon–carbon double bond, which could isomerize to the thermodynamically more stable endocyclic enone (Scheme 2). Depending on which hydroxyl group of **12** acts as the leaving group in this fragmentation reaction, both enones **11a** or **11b** can be formed, thus explaining their formation from diastereopure mesylate **10a**. In fact, we could demonstrate experimentally, the conversion of diol **12** to a mixture containing enones **11a** and **11b** on reaction with silica gel in 1,2-dibromoethane for 6 h. According to a referee's comment the diastereomeric preference of compound **11a** relative to **11b** (ratio of 34:11) could be explained taking into account the presence of the MsNH group at C6 which is *syn* to the OH group at position C1 in compound **12**, which could favor the formation of **11a** relative to **11b** by stabilizing the C1 carbocation resulting from OH dissociation. Similar results were obtained in the fragmentation of mesylate **10b**. Thus, treatment of diastereopure **10b** with silica gel in DCE under reflux for 35 min led to the desired enone **11b** in 74% yield, while the same reaction in refluxing 1,2-dibromoethane for 45 min afforded a mixture of enones **11b** (45–51% yield) and **11a** (7–8% yield) and diol **12** (9–25% yield). We had previously observed[1] a similar transformation from a related bicyclic enone to give an adamantane-1,3-diamine.

Friedländer condensation of enone **11a** with 4-chloro-2-aminobenzonitrile in the presence of $AlCl_3$ in refluxing DCE for 15 h afforded a mixture of the desired 13-methanesulfonamido-substituted huprine **4a** and its *syn*-regioisomer **13a** in the ratio of 86:14 (^{1}H NMR) in 59% yield (Scheme 3). The presence of the regioisomeric **13a** was detected by the observation of the signal corresponding to its olefinic proton 10-H (δ 5.82 ppm), clearly differentiated from that of the corresponding proton of **4a** (δ 5.48 ppm).[3] This mixture could not be separated by silica gel column chromatography and was submitted to isomerization by treatment with triflic acid in anhydrous dioxane,

thus obtaining essentially pure huprine **4a** (74% yield), which was quantitatively transformed into the corresponding hydrochloride (44% overall yield from **11a**). Similarly, from enone **11b**, a mixture of huprine **4b** and its *syn*-regioisomer **13b**, was obtained in 71% yield. However, in this case, pure **4b** (51% pure product) could be isolated by silica gel column chromatography, which was quantitatively transformed into the corresponding hydrochloride. The intermediate formation of *syn*-huprines during the Friedländer condensation leading to *anti*-huprines had been previously clearly established, in spite of the absence of *syn*-huprines in the final product of many of such reactions.[3,12]

Worthy of note, the overall yield of the mixture of huprines **4a** and **13a** from mesylate **10a** increased from 49 to 62% when **10a** was submitted to the usual fragmentation reaction conditions in DCE and the DCE-solution of the corresponding enone was used as such in the Friedländer reaction. Similarly, the yield of the mixture of **4b** and **13b** from **10b** increased from 52.5 to 68%.

All of the new compounds have been fully characterized on the basis of IR, ^{1}H and ^{13}C NMR spectra and elemental analysis. Compounds **10a** and **10b** have also been characterized by X-ray diffraction analysis. Assignment of the NMR spectra was performed with the aid of COSY ^{1}H/^{1}H, HETCOR ^{1}H/^{13}C and n.O.e. experiments and by comparison with related compounds.[1,2,5] The observation of cross-peaks in the COSY ^{1}H/^{1}H spectra corresponding to W-couplings was conclusive for the differentiation between the *endo*/*exo* pairs of protons. The assignment of the NMR spectra of ketone **7** is included to correct the previously described,[10] carried out on the basis of tabulated data.

3. Conclusion

In conclusion, new huprines functionalized at position 13 (methylene bridge) with a methanesulfonamido substituent have been synthesized. Introduction of the amino functionality at position 13 was carried out by non-stereoselective reduction of an intermediate oxime function which, after separation of the stereoisomers in a later stage, allowed the preparation of both stereoisomers of the final product **4**. Stereoisomeric *syn*-huprines, **13**, were formed in greater ratio than usual, although in one case efficient chromatographic isolation of the *anti*-huprine (**4b**) could be effected while easy triflic acid isomerization to the corresponding *anti*-huprine (**4a**) could be performed in the other case. Work is in progress to prepare other 13-amido-substituted huprines, whose AChE inhibitory activity, together with that of **4a** and **4b**, will be evaluated and published elsewhere.

4. Experimental

4.1. General

Melting points were determined in open capillary tubes with a MFB 595010M Gallenkamp melting point apparatus. NMR spectra were recorded on the following spectrometers: 500 MHz ^{1}H NMR: Varian Inova 500; 400 MHz ^{1}H NMR and 100.6 MHz ^{13}C NMR: Varian Mercury 400; 75.4 MHz ^{13}C NMR: Varian Gemini 300. The chemical shifts are reported in ppm (δ scale) relative to internal TMS, and coupling constants are reported in hertz (Hz). Assignment of the NMR spectra was carried out on the basis of COSY ^{1}H/^{1}H (standard procedures), HETCOR ^{1}H/^{13}C experiments (HMQC sequence with an indirect detection probe), and n.O.e. experiments. The *endo*/*exo* notation of the methylenic protons at positions 2, 4, 6 and 8 in diketone **5** has been retained for the corresponding protons in compounds **6**–**10** and **12**. The *syn* (*anti*) notation of compound **10b** (**10a**) means that the methanesulfonamido group is on the same (different) side of the mesyloxy function. The *syn*/*anti* notation of the methanesulfonamido group of **10b** and **10a** has been retained in the related compounds **4b**, **9b** and **11b**, and **4a**, **9a** and **11a**, respectively. IR spectra were run on a FT/IR Perkin–Elmer model 1600 spectrophotometer. Absorption values are expressed as wave-numbers (cm^{-1}); only significant absorption bands are given. MS spectrum of compound **12** was taken on a Hewlett–Packard 5988A spectrometer with direct introduction of the sample. Silica gel 60 AC.C (70–200 mesh, SDS, ref 2100027) was used without any pretreatment for the fragmentation reactions and column chromatography. Thin-layer chromatography (TLC) was performed with aluminum-backed sheets (about 8 cm height) with silica gel 60 F_{254} (Merck, ref 1.05554), and the spots were visualized with UV light and 1% aqueous solution of $KMnO_4$. Analytical grade solvents were used for recrystallizations, while pure for synthesis solvents were used in the reactions, extractions and column chromatography. NMR spectra were performed at the Serveis Científico-Tècnics of the University of Barcelona, while elemental analyses were carried out at the Mycroanalysis Service of the IIQAB (CSIC, Barcelona, Spain).

4.1.1. 6,6-(Ethylenedioxy)-3-methyl-2-oxa-1-adamantanol (6). $CeCl_3{\cdot}7H_2O$ (27.4 g, 73.5 mmol) was dried at 160°C/1 Torr for 16 h and added to anhydrous THF (365 mL). The suspension was stirred at room temperature for 2 h, cooled to −78°C, and treated with a solution of MeMgBr (3 M solution in Et_2O, 19.5 mL, 58.5 mmol). The mixture was stirred at −78°C for 1 h and treated dropwise with a solution of diketone **5** (5.00 g, 23.8 mmol) in anhydrous THF (100 mL). The reaction mixture was stirred at −78°C for 1 h, allowed to warm to room temperature over 3 h, stirred at room temperature for 12 h, and treated with saturated aqueous NH_4Cl (190 mL). The organic layer was separated and concentrated in vacuo, and the resulting wet white solid residue was taken up in AcOEt (180 mL). The organic solution was dried over Na_2SO_4 and evaporated at reduced pressure, to give oxaadamantanol **6** (5.10 g, 95% yield) as a white solid. The analytical sample was obtained by crystallization: mp 143–144°C (AcOEt); R_f 0.27 (SiO_2, hexane/AcOEt 1:1); IR (KBr) 3293; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (s, 3H, 3-CH_3), 1.61 [broad d, $J\approx$12.8 Hz, 2H, 4(10)-H_{endo}], 1.66 [broad d, J=12.2 Hz, 2H, 8(9)-H_{endo}], 1.83 [broad d, J=12.8 Hz, 2H, 4(10)-H_{exo}], 2.07 [broad s, 2H, 5(7)-H], 2.13 [broad d, J=12.2 Hz, 2H, 8(9)-H_{exo}], 3.82 (s, 1H, OH), 3.96–3.99 (complex signal, 4H, O–CH_2–CH_2–O); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 27.8 (CH_3, 3-CH_3), 37.0 [CH, C5(7)], 38.6 [CH_2, C4(10)], 38.7 [CH_2, C8(9)], 64.49 (CH_2) and 64.53 (CH_2) (O–CH_2–CH_2–O), 73.8 (C, C3), 94.3 (C, C1), 109.4 (C, C6). Anal. calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63,33; H, 8.11.

4.1.2. 1-Hydroxy-3-methyl-2-oxaadamantan-6-one[10] (7). To a solution of oxaadamantanol **6** (5.12 g, 22.7 mmol) in dioxane (500 mL), 2N HCl (145 mL) was added, and the reaction mixture was heated under reflux overnight, and concentrated in vacuo. The resulting residue was diluted with water (100 mL) and extracted with CH_2Cl_2 (5×200 mL). The combined organic extracts were dried over Na_2SO_4 and evaporated at reduced pressure, to give a brown solid residue consisting mainly of ketone **7**, which was submitted to flash chromatography (SiO_2, 150 g, hexane/AcOEt mixtures). On elution with mixtures hexane/AcOEt from 40:60 to 20:80, a mixture of starting **6** and ketone **7** in an approximate ratio of 1:3 (^{1}H NMR, 720 mg), and pure ketone **7** (2.60 g, 63% yield; 75% total yield) were successively isolated. The analytical sample of **7** was obtained by crystallization: R_f 0.15 (SiO_2, hexane/AcOEt 1:1). White solid: mp 156–158°C (AcOEt); described: 136–139°C (diethyl ether).[10] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (s, 3H, 3-CH_3), 1.95 [dm, J=13.2 Hz, 2H, 4(10)-H_{endo}], superimposed in part 2.01 [dm, $J\approx$13.2 Hz, 2H, 4(10)-H_{exo}], 2.05 [dm, $J\approx$12.4 Hz, 2H, 8(9)-H_{endo}], 2.22 [dm, $J\approx$12.4 Hz, 2H, 8(9)-H_{exo}], 2.73 [broad s, 2H, 5(7)-H], 4.28 (s, 1H, OH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 27.1 (CH_3, 3-CH_3), 41.7 [CH_2, C8(9)], 42.6 [CH_2, C4(10)], 44.9 [CH, C5(7)], 74.2 (C, C3), 93.9 (C, C1), 215.4 (C, C6).

4.1.3. 1-Hydroxy-3-methyl-2-oxaadamantan-6-one oxime (8). Hydroxylamine hydrochloride (5.04 g, 72.5 mmol) and a mixture of anhydrous Na_2CO_3/K_2CO_3 1:1 (13.1 g, 61.8 mmol of Na_2CO_3 and 47.5 mmol of K_2CO_3) were added to a solution of ketone **7** (2.58 g, 14.2 mmol) in dioxane (85 mL), and the reaction mixture was heated under reflux overnight. The resulting suspension was filtered in vacuo, washing with hot dioxane (2×15 mL). The combined filtrates were evaporated at reduced pressure, to give oxime **8** (2.80 g, quantitative yield) as a white solid. The analytical sample was obtained by crystallization: mp 225–226°C (AcOEt/isopropanol 3:2); R_f 0.36 (SiO_2, AcOEt); IR (KBr) 3364, 1664; ^{1}H NMR (500 MHz, CD_3OD) δ 1.19 (s, 3H, 3-CH_3), 1.64 (ddd, J=13.0 Hz, J'=3.5 Hz, J''=1.0 Hz, 1H, 10-H_{endo}), superimposed in part 1.67 (ddd, J=13.0 Hz, J'=3.5 Hz, J''=1.5 Hz, 1H, 4-H_{endo}), 1.74 (ddd, J=13.0 Hz, J'=J''=3.0 Hz, 1H, 10-H_{exo}), 1.76–1.84 (complex signal, 4H, 4-H_{exo}, 8-H_{exo}, 8-H_{endo} and 9-H_{endo}), 1.87 (dddd, J=12.0 Hz, J'=J''=3.0 Hz, J'''=1.0 Hz, 1H, 9-H_{exo}), 2.78 (m, 1H, 5-H), 3.80 (m, 1H, 7-H), 4.84 (s, 1-OH, N-OH); ^{13}C NMR (100.6 MHz, CD_3OD) δ 28.2 (CH_3, 3-CH_3), 29.5 (CH, C7), 37.4 (CH, C5), 41.4 (CH_2, C8), 41.7 (CH_2, C10), 42.8 (CH_2, C9), 43.1 (CH_2, C4), 75.5 (C, C3), 95.0 (C, C1), 163.4 (C, C6). Anal. calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10. Found: C, 60.49; H, 7.66; N, 6.94.

4.1.4. Diastereomeric mixture of 6-amino-3-methyl-2-oxa-1-adamantanol (9). To a solution of $NiCl_2{\cdot}6H_2O$ (494 mg, 2.08 mmol) in MeOH (40 mL), $NaBH_4$ (236 mg, 6.24 mmol) was added in portions over 5 min. The resulting black suspension was stirred thoroughly for 30 min, and a solution of oxime **8** (820 mg, 4.16 mmol) in MeOH (10 mL), and then $NaBH_4$ (552 mg, 14.6 mmol, in portions over 5 min) were successively added. The reaction mixture was stirred at room temperature for 1 h, and was filtered through a short pad of Celite™, washing the solid with MeOH (25 mL). The filtrate was evaporated in vacuo, and the green solid residue was taken up in 2N HCl (20 mL). The resulting solution was stirred at room temperature for 30 min, washed with CH_2Cl_2 (5×40 mL), made alkaline with KOH pellets, and concentrated in vacuo. The resulting residue was extracted with hot CH_2Cl_2 (6×50 mL), and the combined organic extracts were dried over Na_2SO_4, and evaporated at reduced pressure, to afford a mixture of diastereomeric amines **9** in an approximate ratio **9a/9b** of 1.1:1 (^{1}H and ^{13}C NMR) (590 mg, 78% yield). An analytical sample of **9** was obtained by crystallization, mp 164–166°C (AcOEt/isopropanol in the ratio of 2:1); IR (KBr) 3600–2400 (max. at 3351 and 3281); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (s, 3H, 3-CH_3), 1.43–1.57 (complex signal), 1.69–1.85 (complex signal) and 1.98–2.16 (complex signal) (total 11H, methylene protons, 5(7)-H and OH], 2.25 (broad signal, 2H, NH_2), 3.00 (m) and 3.10 (m) (total 1H, 6-H); ^{13}C NMR (75.4 MHz, CD_3OD), signals of the main diastereomer **9a**: δ 29.0 (CH_3, 3-CH_3), 35.2 [CH_2, C4(10)], 36.7 [CH, C5(7)], 41.9 [CH_2, C8(9)], 53.7 (CH, C6), 75.2 (C, C3), 94.6 (C, C1); signals of the minor diastereomer **9b**: δ 28.5 (CH_3, 3-CH_3), 35.6 [CH_2, C8(9)], 37.2 [CH, C5(7)], 42.0 [CH_2, C4(10)], 53.6 (CH, C6), 74.7 (C, C3), 94.8 (C, C1). Anal. calcd for $C_{10}H_{17}NO_2{\cdot}1/4\ H_2O$: C, 63.97; H, 9.40; N, 7.46. Found: C, 63.65; H, 9.03; N, 7.09.

4.1.5. *anti*- and *syn*-6-Methanesulfonamido-3-methyl-2-oxa-1-adamantyl methanesulfonate (10a) and (10b). A solution of a diastereomeric mixture of amines **9** (3.04 g, 16.6 mmol) and anhydrous Et_3N (8.1 mL, 5.88 g, 58.1 mmol) in anhydrous CH_2Cl_2 (145 mL) was cooled to −10°C. Methanesulfonyl chloride (4.80 mL, 7.11 g, 62.1 mmol) was added dropwise over a period of 5 min, and the reaction mixture was stirred at −10°C for 30 min. The mixture was poured into a mixture of 10% aqueous HCl (145 mL) and crushed ice. The organic layer was separated, and the aqueous one was extracted with CH_2Cl_2 (4×170 mL). The combined organic extracts were washed successively with saturated aqueous $NaHCO_3$ (2×120 mL) and brine (120 mL), dried over Na_2SO_4, and evaporated at reduced pressure, to give a residue (6.75 g), which was submitted to column chromatography (SiO_2, 260 g, hexane/AcOEt mixtures). All fractions contained mixtures of **10a** and **10b** in different ratios, the first ones enriched in **10b** and the last ones in **10a** (4.93 g, 88% total yield of **10a** plus **10b**, 47% of **10a** and 41% of **10b**). Recrystallization from AcOEt of mixtures enriched in either **10a** or **10b** afforded significant amounts of diastereopure **10a** and **10b**.

Compound **10a**. White solid; mp 117–119°C (AcOEt); R_f 0.12 (SiO_2, hexane/AcOEt 1:1); IR (KBr) 3302, 1361, 1346, 1175, 1150; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (s, 3H, 3-CH_3), 1.63 [broad d, J=13.6 Hz, 2H, 4(10)-H_{endo}], 1.76 [broad d, $J\approx$13.6 Hz, 2H, 4(10)-H_{exo}], 2.06 [dm, J=12.0 Hz, 2H, 8(9)-H_{exo}], 2.31 [dm, $J\approx$12.0 Hz, 2H, 8(9)-H_{endo}], 2.42 [m, 2H, 5(7)-H], 3.01 (s, 3H, C$H_3$$SO_2$NH), 3.16 (s, 3H, CH_3SO_3), 3.63 (m, 1H, 6-H), 5.45 (d, J=6.4 Hz, 1H, CH_3SO_2N*H*); ^{13}C NMR (75.4 MHz, $CDCl_3$+CD_3OD) δ 27.6 (CH_3, 3-CH_3), 33.8 [CH_2, C4(10)], 34.4 [CH, C5(7)], 38.9 [CH_2, C8(9)], 40.5 (CH_3, CH_3SO_2NH), 41.8 (CH_3, CH_3SO_3), 54.0 (CH, C6), 76.6 (C, C3), 105.9 (C, C1). Anal. calcd for $C_{12}H_{21}NO_6S_2$: C, 42.46; H, 6.24; N, 4.13; S, 18.89. Found: C, 42.48; H, 6.39; N, 4.13; S, 18.87. *Compound* **10b**.

White solid; mp 109–110°C (AcOEt); R_f 0.14 (SiO_2, hexane/AcOEt 1:1); IR (KBr) 3267, 1361, 1329, 1175, 1144; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (s, 3H, 3-CH_3), 1.66 [broad dd, J=12.0 Hz, J'=2.4 Hz, 2H, 4(10)-H_{exo}], 1.85 [dm, $J\approx$12.0 Hz, 2H, 4(10)-H_{endo}], 2.15 [complex signal, 4H, 8(9)-H_{exo} and 8(9)-H_{endo}], 2.46 [m, 2H, 5(7)-H], 3.01 (s, 3H, C$H_3$$SO_2$NH), 3.17 (s, 3H, CH_3SO_3), 3.61 (dt, J=6.0 Hz, J'=2.8 Hz, 1H, 6-H), 5.11 (d, J=6.0 Hz, 1H, CH_3SO_2NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 27.5 (CH_3, 3-CH_3), 34.0 [CH_2, C8(9)], 35.2 [CH, C5(7)], 39.8 [CH_2, C4(10)], 41.9 (CH_3, CH_3SO_2NH), 42.1 (CH_3, CH_3SO_3), 54.4 (CH, C6), 76.2 (C, C3), 106.3 (C, C1). Anal. calcd for $C_{12}H_{21}NO_6S_2$: C, 42.46; H, 6.24; N, 4.13; S, 18.89. Found: C, 42.61; H, 6.10; N, 4.07; S, 18.97.

4.1.6. *anti*-9-Methanesulfonamido-7-methylbicyclo[3.3.1]non-6-en-3-one (11a). *Method 1*. A suspension of mesylate **10a** (400 mg, 1.18 mmol) and silica gel (283 mg) in DCE (5 mL) was heated under reflux for 35 min with vigorous stirring. After concentrating in vacuo, the resulting residue was extracted with hot CH_2Cl_2 (3×10 mL), and the combined organic extracts were evaporated at reduced pressure, to give enone **11a** (238 mg, 83% yield) as an oil that crystallized on standing. An analytical sample was obtained by crystallization: mp 156–159°C (AcOEt); R_f 0.43 (SiO_2, AcOEt); IR (KBr) 3281, 1720, 1314, 1154; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.64 (s, 3H, 7-CH_3), 1.87 (broad d, J=19.0 Hz, 1H, 8-H_{endo}), 2.29 (ddd, J=15.5 Hz, $J'\approx$3.0 Hz, $J''\approx$2.0 Hz, 1H, 2-H_{endo}), 2.35 (ddd, J=14.5 Hz, J'=J''=3.0 Hz, 1H, 4-H_{endo}), 2.43 (broad dd, J=19.0 Hz, J'=6.5 Hz, 1H, 8-H_{exo}), 2.55–2.65 (complex signal, 3H, 1-H, 2-H_{exo} and 4-H_{exo}), 2.67 (m, 1H, 5-H), 3.02 (s, 3H, C$H_3$$SO_2$NH), 4.05 (dm, J=9.0 Hz, 1H, 9-H), 4.68 (d, J=9.0 Hz, 1H, CH_3SO_2NH), 5.34 (dm, J=4.0 Hz, 1H, 6-H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 23.1 (CH_3, 7-CH_3), 32.7 (CH_2, C8), 34.4 (CH, C1), 37.0 (CH, C5), 41.9 (CH_3, CH_3SO_2NH), 45.4 (CH_2, C4), 47.7 (CH_2, C2), 52.7 (CH, C9), 120.7 (CH, C6), 134.5 (C, C7), 208.8 (C, C3). Anal. calcd for $C_{11}H_{17}NO_3S\cdot0.25H_2O$: C, 53.31; H, 7.12; N, 5.65; S, 12.94. Found: C, 53.15; H, 6.98; N, 5.50; S, 12.96.

Method 2. A suspension of mesylate **10a** (200 mg, 0.59 mmol) and silica gel (140 mg) in 1,2-dibromoethane (2.5 mL) was heated under reflux for 45 min with vigorous stirring. After concentrating at reduced pressure, the resulting residue was submitted to column chromatography (SiO_2, 4 g, hexane/AcOEt/MeOH mixtures). On elution with hexane/AcOEt 60:40 and 50:50, a mixture of enones **11b** and **11a** in the ratio of 2:3 (5 mg, 2 mg of **11b**, 1% yield), and enone **11a** (80 mg, 56% total yield) were successively isolated. On elution with AcOEt, adamantanediol **12** (40 mg, 26% yield) was isolated as a light brown oil, which solidified on standing. An analytical sample of **12** was obtained by crystallization: white crystals, mp 203–206°C (isopropanol); R_f 0.05 (SiO_2, AcOEt); IR (KBr) 3312, 1337, 1133; ^{1}H NMR (500 MHz, CD_3OD) δ 1.45 [broad d, J=13.0 Hz, 2H, 8(9)-H_{endo}], 1.66 [dm, $J\approx$12.0 Hz, 2H, 4(10)-H_{endo}], 1.69 (broad s, 2H, 2-H_{exo} and 2-H_{endo}), 1.75 [broad d, J=12.0 Hz, 2H, 4(10)-H_{exo}], 1.90 [broad d, $J\approx$13.0 Hz, 2H, 8(9)-H_{exo}], 2.26 [m, 2H, 5(7)-H], 2.95 (s, 3H, C$H_3$$SO_2$NH), 3.36 (m, 1H, 6-H), 4.84 (s, OH and CH_3SO_2NH); ^{13}C NMR (75.4 MHz, CD_3OD) δ 37.3 [CH, C5(7)], 38.5 [CH_2, C8(9)], 40.6 (CH_3, CH_3SO_2NH), 43.8 [CH_2, C4(10)], 53.3 (CH_2, C2), 56.9 (CH, C6), 69.90 (C) and 69.94 (C) (C1 and C3). MS (EI), significant ions: m/z (relative intensity) 261 (2, $M^{\cdot+}$), 243 [5, $(M-H_2O)^{\cdot+}$], 182 [28, $M-CH_3SO_2)^+$], 164 [23, $(M-H_2O-CH_3SO_2)^+$], 148 [18, $(M-2OH-CH_3SO_2)^+$], 111 (100). Anal. calcd for $C_{11}H_{19}NO_4S\cdot0.75H_2O$: C, 48.07; H, 7.52; N, 5.10; S, 11.66. Found: C, 47.97; H, 7.30; N, 4.89; S, 11.83.

4.1.7. *syn*-9-Methanesulfonamido-7-methylbicyclo[3.3.1]non-6-en-3-one (11b). It was prepared as described for **11a** (Method 1), starting from a suspension of mesylate **10b** (235 mg, 0.69 mmol) and silica gel (164 mg) in DCE (3 mL). After concentrating in vacuo, the obtained residue was extracted with hot CH_2Cl_2 (3×6 mL). Evaporation of the solvent from the combined organic extracts gave an oily residue, which was triturated with diethyl ether (3×4 mL) to give an enone **11b** (124 mg, 74% yield) as a white solid. An analytical sample of **11b** was obtained by crystallization: mp 142–143°C (AcOEt); R_f 0.43 (SiO_2, AcOEt); IR (KBr) 3286, 1716, 1335, 1152; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.60 (s, 3H, 7-CH_3), 1.96 (broad d, J=18.0 Hz, 1H, 8-H_{endo}), 2.18 (dm, J=16.0 Hz, 1H, 2-H_{endo}), 2.23 (ddd, J=15.5 Hz, $J'\approx J''\approx$2.0 Hz, 1H, 4-H_{endo}), 2.52 (broad dd, J=18.0 Hz, J'=6.5 Hz, 1H, 8-H_{exo}), 2.59 (ddm, $J\approx J'\approx$6.5 Hz, 1H, 1-H), 2.64 (ddd, $J\approx$16.0 Hz, J'=6.5 Hz, J''=1.0 Hz, 1H, 2-H_{exo}), superimposed in part 2.67 (dd, J=15.5 Hz, J'=4.0 Hz, 1H, 4-H_{exo}), 2.77 (m, 1H, 5-H), 3.04 (s, 3H, C$H_3$$SO_2$NH), 3.79 (m, 1H, 9-H), 5.23 (d, J=5.5 Hz, 1H, CH_3SO_2NH), 5.38 (dm, J=6.0 Hz, 1H, 6-H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 22.6 (CH_3, 7-CH_3), 35.6 (CH, C1), 36.2 (CH, C5), 38.5 (CH_2, C8), 40.4 (CH_2, C4), 41.0 (CH_3, CH_3SO_2NH), 43.8 (CH_2, C2), 52.4 (CH, C9), 123.7 (CH, C6), 133.0 (C, C7), 210.2 (C, C3). Anal. calcd for $C_{11}H_{17}NO_3S$: C, 54.30; H, 7.04; N, 5.76; S, 13.18. Found: C, 54.32; H, 7.30; N, 5.78; S, 12.96.

Note. When this reaction was carried out in refluxing 1,2-dibromoethane (9 mL) for 45 min, as described for **11a** (Method 2), from mesylate **10b** (600 mg, 1.77 mmol) and silica gel (420 mg), enone **11b** (53 mg), a mixture of enones **11b** and **11a** in the ratio of 84:16 (GC, 199 mg, 51% total yield of **11b** and 7% yield of **11a**) and adamantanediol **12** (44 mg, 10% yield) were obtained, after column chromatography.

4.1.8. Formation of a mixture of 11a and 11b from 12. A suspension of diol **12** (104 mg, 0.40 mmol) and silica gel (85 mg) in 1,2-dibromoethane (2 mL) was heated under reflux for 6 h. The mixture was concentrated in vacuo and the obtained residue was extracted with CH_2Cl_2 (3×5 mL). Concentration of the combined organic extracts at reduced pressure gave a residue (45 mg) containing the starting compound and enones **11a** and **11b** (^{1}H NMR, 34:11 relative area of **11a** and **11b** by GC).

4.1.9. 12-Amino-3-chloro-6,7,10,11-tetrahydro-*anti*-13-methanesulfonamido-9-methyl-7,11-methanocycloocta[*b*]quinoline hydrochloride (4a·HCl). *Mixture of **4a** and its regioisomer **13a***. To a suspension of anhydrous $AlCl_3$ (221 mg, 1.66 mmol) and 2-amino-4-chlorobenzonitrile (freshly sublimed at 100–110°C/1 Torr, 261 mg, 1.71 mmol) in DCE (3.5 mL) was added a solution of

enone **11a** (238 mg, 0.98 mmol) in DCE (14 mL) dropwise. The reaction mixture was stirred under reflux for 15 h, allowed to cool to room temperature, diluted with water (8 mL) and THF (8 mL), made basic by addition of 5N NaOH (1.2 mL), and stirred at room temperature for 40 min. The organic solvents were removed under reduced pressure, and the resulting mixture was filtered in vacuo, washing the solid with water (2×5 mL) to give, after drying, a yellowish solid residue (444 mg), consisting mainly of **4a**. The filtrate was extracted with CH_2Cl_2 (3×40 mL), and the combined organic extracts were dried over Na_2SO_4, and evaporated at reduced pressure, to give a residue (38 mg), which did not contain **4a**. The yellow solid was submitted to flash chromatography (SiO_2, 13 g, hexane/AcOEt mixtures). On elution with AcOEt, **4a** impurified with its *syn*-regioisomer **13a** (219 mg, 59% yield of **4a** plus **13a** in the ratio of 86:14 by ^{1}H NMR) was isolated.

Note. When this reaction was performed starting from **10a** (300 mg, 0.88 mmol), which was submitted to the reaction conditions of Method 1 of Section 4.1.6, and the resulting mixture of **11a** and silica gel in DCE (3.5 mL) was diluted with the same solvent (9 mL) and reacted with 2-amino-4-chlorobenzonitrile (235 mg, 1.54 mmol), as described above under this Section a mixture of **4a** and **13a** in the ratio of 9:1 (^{1}H NMR) was obtained, after column chromatography (208 mg, 62% overall yield of **4a** plus **13a**, from **10a**).

*Triflic acid isomerization of the mixture of **4a** and **13a***. Triflic acid (183 μL, 315 mg, 2.1 mmol) was added to a solution of the above mixture of **4a** and **13a** in the ratio of 86:14 (219 mg, 0.58 mmol) in anhydrous 1,4-dioxane (11 mL) and the mixture was heated at 93°C for 24 h under an argon atmosphere. The reaction mixture was allowed to cool to room temperature and was concentrated in vacuo. The obtained residue was taken in CH_2Cl_2 (25 mL) and washed with 10% aqueous $NaHCO_3$ (25 mL). The aqueous phase was extracted with CH_2Cl_2 (4×35 mL) and the combined organic phases were dried (Na_2SO_4) and concentrated in vacuo to give a yellow solid consisting mainly of **4a** (^{1}H NMR, 162 mg, 74% yield).

*Hydrochloride of **4a***. A solution of **4a** (155 mg, 0.41 mmol) in methanol (4 mL) was treated with excess of a methanolic solution of anhydrous 0.45 M HCl (2.86 mL, 1.29 mmol). Concentration of the solution in vacuo gave **4a**·HCl as a yellow solid residue (169 mg, quantitative yield). The analytical sample was obtained by crystallization from isopropanol followed by drying of the solid material under reduced pressure (3 Torr) and 40°C for 2 days, mp 233–235°C (decomposition) (isopropanol). It contains 1.25 mol water and 0.05 mol isopropanol per mol **4a**·HCl; R_f (**4a**, free base) 0.18 (SiO_2, AcOEt/MeOH 9:1); IR (KBr) 3500–2500 (max at 3376, 3207, 2918), 1654, 1641, 1587, 1308, 1150; ^{1}H NMR (500 MHz, CD_3OD) δ 1.63 (s, 3H, 9-CH_3), 1.94 (broad d, J=18.5 Hz, 1H, 10-H_{endo}), 2.70 (ddm, $J\approx$18.5 Hz, J'=5.0 Hz, 1H, 10-H_{exo}), 2.78 (m, 1H, 7-H), 3.00 (dd, J=17.5 Hz, J'=1.5 Hz, 1H, 6-H_{endo}), 3.07 (s, 3H, C$H_3$$SO_2$-NH), 3.42–3.48 (complex signal, 2H, 11-H and 6-H_{exo}), 3.84 (m, 1H, 13-H), 4.84 (s, NH_2, NH^+ and CH_3SO_2NH), 5.48 (dm, J=4.5 Hz, 1H, 8-H), 7.60 (dd, J=9.0 Hz, J'=2.0 Hz, 1H, 2-H), 7.75 (d, J=2.0 Hz, 1H, 4-H), 8.36 (d, J=9.0 Hz, 1H, 1-H). ^{13}C NMR (75.4 MHz, CD_3OD) δ 23.4 (CH_3, 9-CH_3), 31.0 (CH_2, C10), 32.6 (CH, C11), 34.0 (CH, C7), 36.7 (CH_2, C6), 41.5 (CH_3, CH_3SO_2NH), 51.6 (CH, C13), 114.5 (C, C11a), 115.0 (C, C12a), 119.1 (CH, C4), 121.5 (CH, C8), 126.4 (CH, C1), 127.7 (CH, C2), 135.7 (C, C9), 139.5 (C, C4a), 140.5 (C, C3), 151.7 (C) and 156.8 (C) (C5a and C12). Anal. calcd for $C_{18}H_{20}ClN_3O_2S$·HCl·1.25H_2O·0.05C_3H_8O: C, 49.56; H, 5.48; N, 9.55; S, 7.29; Cl, 16.12. Found: C, 49.86; H, 5.26; N, 9.26; S, 7.07; Cl, 15.91.

4.1.10. 12-Amino-3-chloro-6,7,10,11-tetrahydro-*syn*-13-methanesulfonamido-9-methyl-7,11-methanocycloocta[*b*]quinoline hydrochloride (4b·HCl). *Preparation of **4b***. It was prepared as described for **4a**, starting from a suspension of anhydrous $AlCl_3$ (185 mg, 1.39 mmol) and 2-amino-4-chlorobenzonitrile (218 mg, 1.43 mmol) in DCE (3 mL), and a solution of enone **11b** (200 mg, 0.82 mmol) in DCE (12 mL), obtaining a yellowish solid (311 mg), consisting mainly of **4b**. The filtrate was extracted with CH_2Cl_2 (3×15 mL), and the combined organic extracts were dried over Na_2SO_4, and evaporated at reduced pressure, to give an oil (59.7 mg), which contained impure **4b**. Both, the yellow solid and the oil were separately submitted to flash chromatography (Table 1). In the first case (SiO_2, 11 g, hexane/AcOEt mixtures), on elution with hexane/AcOEt 25:75 and with AcOEt, pure **4b** (158 mg, 51% yield) and also **4b** impurified with 8% of its *syn*-regioisomer **13b** (29 mg, ^{1}H NMR) were successively isolated. In the second case (SiO_2, 2.3 g), on elution with hexane/AcOEt 25:75, **4b** impurified with 8% of its *syn*-regioisomer **13b** was isolated (34 mg) (71% total yield of **4b** and **13b**).

Note. When this reaction was performed starting from **10b** (300 mg, 0.88 mmol), which was submitted to the reaction conditions of Section 4.1.7, and the obtained mixture of **11b** and silica gel in DCE (3.5 mL) was diluted with the same solvent (9 mL) and reacted with 2-amino-4-chlorobenzonitrile (235 mg, 1.54 mmol), as described under this heading, pure **4b** (160 mg) and a mixture of **4b** and **13b** in the ratio of 93:7 (68 mg) was obtained, after column chromatography (68% overall yield of **4b** plus **13b**, from **10b**).

*Hydrochloride of **4b***. A solution of pure **4b** (60 mg, 0.16 mmol) in MeOH (1 mL) was treated with a solution of HCl in MeOH (0.205 M, 2.30 mL, 0.47 mmol), and the solvent was evaporated at reduced pressure, to give **4b**·HCl (71 mg, quantitative yield) as a yellowish solid: mp 229–233°C (decomposition) (AcOEt/MeOH 8:1); R_f (**4b** free base) 0.21 (SiO_2, AcOEt/MeOH 9:1); IR (KBr) 3500–2500 (max. at 3369, 3182, 2912), 1654, 1632, 1586, 1312, 1149; ^{1}H NMR (500 MHz, CD_3OD) δ1.61 (s, 3H, 9-CH_3), 2.10 (broad d, J=18.0 Hz, 1H, 10-H_{endo}), 2.72 (ddm, J=18.0 Hz, J'=4.5 Hz, 1H, 10-H_{exo}), 2.85 (dm, J=18.0 Hz, 1H, 6-H_{endo}), 2.90 (m, 1H, 7-H), 3.02 (s, 3H, C$H_3$$SO_2$NH), 3.36 (dd, J=18.0 Hz, J'=6.0 Hz, 1H, 6-H_{exo}), 3.45 (m, 1H, 11-H), 3.95 (dd, J=3.5 Hz, J'=3.0 Hz, 1H, 13-H), 4.84 (s, NH_2, NH^+ and CH_3SO_2NH), 5.56 (broad d, J=6.5 Hz, 1H, 8-H), 7.61 (dd, J=9.0 Hz, J'=2.0 Hz, 1H, 2-H), 7.76 (d, $J\approx$2.0 Hz, 1H, 4-H), 8.36 (d, J=9.0 Hz, 1H, 1-H). ^{13}C NMR (75.4 MHz, CD_3OD) δ 22.9 (CH_3, 9-CH_3), 30.8 (CH_2, C6), 33.3 (CH, C7), 33.4 (CH, C11), 36.9 (CH_2, C10), 40.9

(CH_3, CH_3SO_2NH), 52.4 (CH, C13), 111.9 (C, C11a), 115.3 (C, C12a), 119.2 (CH, C4), 124.5 (CH, C8), 126.3 (CH, C1), 127.7 (CH, C2), 134.9 (C, C9), 139.5 (C, C4a), 140.6 (C, C3), 152.1 (C) and 157.6 (C) (C5a and C12). Anal. calcd for $C_{18}H_{20}ClN_3O_2S{\cdot}HCl{\cdot}0.75H_2O$: C, 48.98; H, 5.48; N, 9.52; S, 7.26; Cl, 16.06. Found: C, 49.23; H, 5.25; N, 9.10; S, 7.01; Cl, 15.95.

4.2. X-Ray crystal-structure determination of 10a (Table 1)[13]

A prismatic crystal was selected and mounted on a MAR345 diffractometer. Unit-cell parameters were determined from automatic centering of 14401 reflections ($3<\theta<31°$) and refined by least-squares method. Intensities were collected with graphite-monochromatized Mo Kα radiation. Reflections were measured in the range $2.17<\theta<31.59$ and were assumed as observed by applying the condition $I>2\sigma(I)$. Lorentz polarization but no absorption corrections were made. The structure was solved by Direct methods, using SHELXS computer program[14] and refined by full-matrix least-squares method with SHELX97[14] computer program. The function minimized was $\sum w[|F_o|^2-|F_c|^2]^2$, where $w=[\sigma^2(I)+(0.0386P)^2+2.0743P]^{-1}$ and $P=(|F_o|^2+2|F_c|^2)/3$; f, f' and f'' were taken from International Tables of X-ray Crystallography.[15] The position of 13 hydrogen atoms were located from a difference synthesis and refined with an overall isotropic temperature factor and 8 hydrogen atoms were computed and refined, using a riding model, with an overall isotropic temperature factor equal to 1.2 times the equivalent temperature factor of the atom to which they are linked.

Table 1. Experimental data of the X-ray crystal-structure determination of compounds **10a** and **10b**.[13]

Compound	**10a**	**10b**
Molecular formula	$C_{12}H_{21}NO_6S_2$	$C_{12}H_{21}NO_6S_2$
Molecular mass	339.42	339.42
Crystal system	Monoclinic	Orthorhombic
Space group	*Cc*	*Pbca*
Cell parameters		
a (Å)	10.1500(10)	16.255(7)
b (Å)	27.6650(10)	11.161(9)
c (Å)	11.2890(10)	16.928(9)
α (°)	90	90
β (°)	100.3750(10)	90
γ (°)	90	90
V (Å^3)	3118.1(4)	3071(3)
Z	8	8
$F(000)$	1440	1440
d (calcd) (Mg m^{-3})	1.446	1.468
Size of crystal (mm)	0.1×0.1×0.2	0.1×0.1×0.2
Measured reflect.	15742	4411
Independent reflect.	4588	4411
Observed reflect.	4395	610
μ (Mo Kα) (mm^{-1})[a]	0.367	0.372
R	0.034	0.037
Rw	0.084	0.045
$\Delta\rho_{max}$[b] (e Å^{-3})	0.273	0.215
$\Delta\rho_{min}$[c] (e Å^{-3})	−0.227	−0.234
Refined parameters	483	200
Max. shift/e.s.d.	0.00	0.00

[a] μ(Mo Kα) linear absorption coefficient. Radiation Mo Kα (λ=0.71069 Å).
[b] Maximun peaks in final difference synthesis.
[c] Minimum peaks in final difference synthesis.

4.3. X-Ray crystal-structure determination of 10b (Table 1)[13]

A prismatic crystal was selected and mounted on an Enraf-Nonius diffractometer. Unit-cell parameters were determined from automatic centering of 25 reflections ($12<\theta<21°$) and refined by least-squares method. Intensities were collected with graphite-monochromatized Mo Kα radiation, using $\omega/2\theta$ scan technique. Reflections were measured in the range $2.41<\theta<29.95$ and were assumed as observed by applying the condition $I>2\sigma(I)$. Three reflections were measured every 2 h as orientation and intensity control; significant intensity decay was not observed. Lorentz polarization but no absorption corrections were made. The structure was solved by Direct methods, using SHELXS computer program[14] and refined by full-matrix least-squares method with SHELX97[14] computer program. The function minimized was $\sum w[|F_o|^2-|F_c|^2]^2$, where $w=[\sigma^2(I)]^{-1}$; f, f' and f'' were taken from International Tables of X-ray Crystallography.[15] The position 4 hydrogen atoms was located from a difference synthesis and refined with an overall isotropic temperature factor and 17 hydrogen atoms were computed and refined, using a riding model, with an isotropic temperature factor equal to 1.2 times the equivalent temperature factor of the atom to which they are linked.

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