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Enantioselective synthesis of tacrine–huperzine A hybrids. Preparative chiral MPLC separation of their racemic mixtures and absolute configuration assignments by X-ray diffraction analysis

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Abstract

A new synthesis of racemic 7-substituted bicyclo[3.3.1]non-6-en-3-ones, *rac*-**4**, whose key-step involves the reaction of a vinyl triflate, *rac*-**7**, with an organometallic reagent, has been developed. This procedure has been applied to the enantioselective synthesis of (+)- and (−)-7-ethylbicyclo[3.3.1]non-6-en-3-one, (+)- and (−)-**4b**, from which both enantiomers of the cholinesterase inhibitor, tacrine–huperzine A hybrid, **9b**, have been obtained. *Rac*-**9b** and its related compounds *rac*-**9a** and *rac*-**10a** were separated into their enantiomers on a preparative scale by medium pressure liquid chromatography (MPLC) using microcrystalline cellulose triacetate as the chiral stationary phase. X-ray diffraction analysis of (−)-**10a** as the *o*-iodobenzoic acid salt, allowed us to establish its absolute configuration and deduce those of other enantiopure tacrine–huperzine A hybrids.

1. Introduction

We recently described[1] a general procedure for the synthesis of 7-alkylbicyclo[3.3.1]non-6-en-3-ones, *rac*-**4**, by silica gel promoted fragmentation of 3-alkyl-2-oxaadamant-1-yl mesylates, as precursors of a new family of cholinesterase inhibitors,[2] which may be considered as tacrine–huperzine A hybrids. Some members of this family such as *rac*-**9a** and *rac*-**9b** have shown higher cholinesterase inhibitory activities than tacrine. In connection with this work we were interested in the preparation of both enantiomers of compounds **9a** and **9b**.

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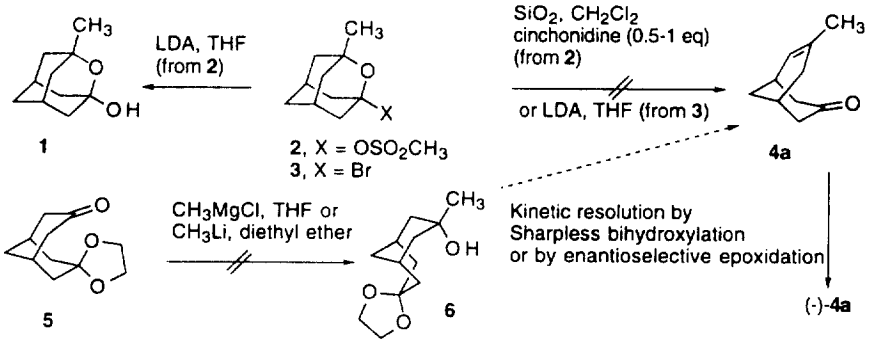
The synthesis of these compounds in enantiopure form was envisaged from the corresponding enantiopure ketones **4a** and **4b**. To this end, we attempted the enantioselective fragmentation of 3-methyl-2-oxaadamant-1-yl mesylate, **2**, by adding cinchonidine to the reaction medium (silica gel, dichloromethane). However, fragmentation of **2** in the presence of 0.5–1.0 eq. cinchonidine did not take place. Attempts to carry out the fragmentation of **2** by reaction with strong bases, such as LDA, led to the formation of the corresponding oxaadamantanol, **1**, probably by an elimination reaction with sulfene formation.[3] Moreover, 1-bromo-3-methyl-2-oxaadamantane,[4] **3**, was recovered unchanged after treatment with a 2 M solution of LDA in THF/heptane/ethylbenzene. These results are in accord with the Grob fragmentation of related substrates which only takes place under acid conditions.[5,6] A potentially enantioselective approach to **4a**, based on the enantioselective dehydration of alcohol **6**, failed because the addition of methylmagnesium chloride or methyllithium to the known[7] monoketal **5** always gave the starting compound, probably because enolate formation was faster than nucleophilic addition (Scheme 1).



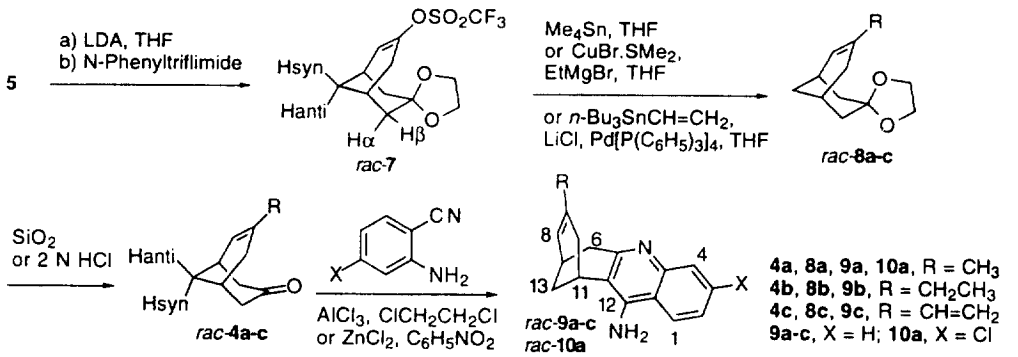
Scheme 1. Unsuccessful potentially enantioselective approaches to 7-methylbicyclo[3.3.1]non-6-en-3-one, **4a**

Attempts to carry out the kinetic resolution of *rac*-**4a** by enantioselective bihydroxylation using the Sharpless procedure[8,9] were discouraging, recovering the starting ketone with very low specific rotation [for the specific rotation of (+)-**4b** (81 e.e.), see later on]. Although Corey et al.[10] were able to carry out the kinetic resolution of allylic 4-methoxybenzoates by enantioselective bihydroxylation, this kind of transformation does not seem to be of wide applicability.[10] Similarly, attempted kinetic resolution of *rac*-**4a** by enantioselective epoxidation using the method of Jacobsen et al.[11,12] left the unreacted ketone with very low specific rotation (Scheme 1).

2. Results and discussion

Finally we were able to develop a new synthesis of racemic ketones **4** (Scheme 2) which could then be carried out in an enantioselective way. Reaction of the known monoketal **5** with LDA in THF/heptane/ethylbenzene gave the corresponding racemic enolate which was trapped by reaction with N-phenyltriflimide[13] to give the corresponding enol triflate, *rac*-**7**, in good yield. We were able to transform this triflate into a mixture of ketal *rac*-**8c** and ketone *rac*-**4c** (51 and 8% isolated yields, respectively, after silica gel column chromatography) by reaction with tributyl(vinyl)tin in the presence of tetrakis(triphenylphosphine)palladium(0) and lithium chloride in THF, according to the procedure described by Stille.[14,15] However, this procedure failed when applied to the preparation of ketal *rac*-**8a** and gave ketal *rac*-**8b** in only 3% yield, in accordance with the lower reactivity of tetramethyltin and tetraethyltin. The synthesis of *rac*-**8b** could be carried out in 58% yield by reaction of *rac*-**7** with an excess (4.5 eq.) of an organocuprate reagent generated *in situ* from ethylmagnesium bromide and the complex

Cu(I) bromide–dimethyl sulfide in THF, following McMurry's procedure[16] optimized by Kant.[17] Acid hydrolysis (2 N HCl, THF) of ketal *rac*-**8b**, gave the corresponding ketone *rac*-**4b** in 64% yield. Ketone *rac*-**4c** was obtained from the crude reaction mixture of the vinylation of *rac*-**7** by hydrolysis under the column chromatography conditions: the column was charged with the crude reaction mixture and was kept for 16 h before elution was started. In this way, *rac*-**8c** and *rac*-**4c** were obtained in 9 and 60% yield, respectively, from *rac*-**7**. It is noteworthy that ketone *rac*-**4c** could not be obtained by our previous procedure.[1]



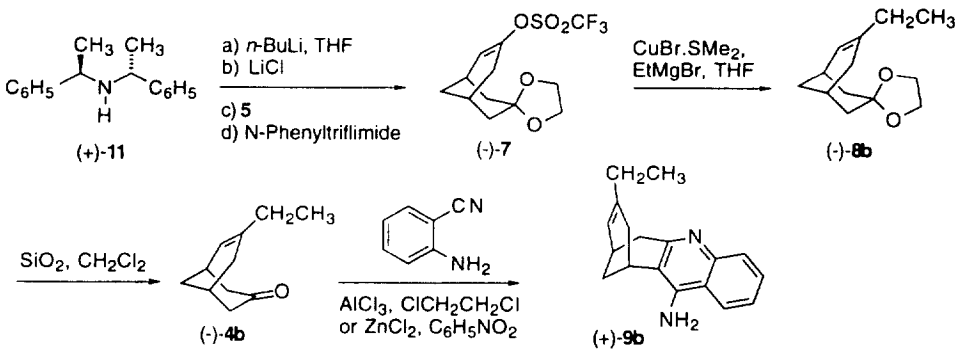
Scheme 2. Potentially enantioselective synthesis of 7-substituted bicyclo[3.3.1]non-6-en-3-ones, *rac*-**4**

Compounds *rac*-**4a** and *rac*-**4b** had been previously transformed into tacrine–huperzine A hybrids *rac*-**9a** and *rac*-**9b**.[2] However, *rac*-**4c** proved to be unstable under the usual Friedländer reaction conditions ($AlCl_3$/1,2-dichloroethane under reflux or $ZnCl_2$/nitrobenzene, 120°C, 2 h) and thus, *rac*-**9c** could not be obtained.

Application of the above procedure to prepare ketones (+)- and (−)-**4b** required the enantioselective deprotonation of monoketal **5** and its trapping under non-racemizing conditions. Simpkins[18] and Koga[19] have prepared enantioselectively trimethylsilyl enol ethers by reaction of prochiral ketones with enantiopure lithium amides in the presence of trimethylsilyl chloride. The amides used may be divided into two groups: those containing a group than can act as an internal ligand for the lithium cation[20] and those lacking such an internal ligand.[21] The optimum stereoselectivities for reactions carried out using internal quenching (the enolate is generated in the presence of a trapping agent such as trimethylsilyl chloride)[22] were attained with amides having internal ligands for the lithium cation in the presence of external additives such as HMPA, or with amides lacking internal ligands in the absence of external additives.[20,21] However, the same reactions carried out under conditions of external quenching (the trapping agent is added after the enolate has been generated) gave lower enantioselectivities. Simpkins et al.[23,24] found that under conditions of external quenching, the addition of lithium chloride allowed the attainment of enantioselectivities of the same order as those obtained under conditions of internal quenching.

According to these previous works, we used the conditions of Simpkins[23,24] to prepare enantioselectively the enolate derived from monoketal **5**. (+)-Bis[(*R*)-1-phenylethyl]amine, (+)-**11**, was transformed into the corresponding amide by reaction with *n*-butyllithium in THF at −78°C, lithium chloride and then monoketal **5** were added at this temperature and the thus formed enolate was trapped by reaction with N-phenyltriflimide at room temperature. In this way (−)-**7** was obtained, after column chromatography, in 64% yield and 81% e.e. established by chiral HPLC using the chiral column Chiralcel OD-H (25×0.46 cm) containing the stationary phase cellulose tris(3,5-dimethylphenylcarbamate). The e.e. of (−)-**7** was in the range of the highest ones previously described[18–24] for similar kinds of transformations (Scheme 3).

Reaction of (−)-**7** with the cuprate generated *in situ* from ethylmagnesium bromide and the complex Cu(I) bromide–dimethyl sulfide as described before for *rac*-**7**, gave (−)-**8b** in 67% yield and 81% e.e.



Scheme 3. Enantioselective synthesis of (−)-**4b** and tacrine–huperzine A hybrid (+)-**9b**

established by chiral GC using the chiral column Supelco BETA-DEX 110® (30 m×0.25 mm) containing the chiral stationary phase β-cyclodextrine. As expected, the e.e. of (−)-**8b** was the same as that of its precursor (−)-**7**.

Similarly, starting from (−)-bis[(*S*)-1-phenylethyl]amine (−)-**11**, (+)-**7** was obtained in 79% yield and 79% e.e., from which (+)-**8b** was obtained in 72% yield and 77% e.e. The small difference in the e.e.s of (+)-**7** and (+)-**8b** is most probably due to analytical errors than to partial epimerization.

Hydrolysis of (+)-**8b** to (+)-**4b** by reaction with 2 N HCl in THF took place with a significant amount of epimerization, which may be easily explained through protonation and deprotonation at the carbon–carbon double bond. However, we were able to carry out this hydrolysis in good yield without epimerization by stirring (+)-**8b** with silica gel in dichloromethane. In a similar way, (−)-**4b** was obtained from (−)-**8b**.

Ketones (+)- and (−)-**4b** were reacted with 2-aminobenzonitrile catalyzed by $AlCl_3$ in 1,2-dichloroethane under reflux giving rise to the corresponding aminoquinolines, which were transformed into the corresponding hydrochlorides and crystallized from methanol/ethyl acetate. From (−)-**4b** [obtained from a triflate (−)-**7** of 79% e.e.], (+)-**9b**·HCl (75% yield, 53% e.e.) was obtained, which on crystallization from methanol/ethyl acetate gave (+)-**9b**·HCl (26% yield, 99% e.e.). The e.e.s of the samples of (+)-**9b**·HCl were established by chiral HPLC on the free base, using the above-cited Chiralcel OD-H column. The specific rotation of (+)-**9b**·HCl (99% e.e.) was quite high $[\alpha]_D^{20}$=+353 (c=0.95, methanol). Similarly, from (+)-**4b** (81% e.e.), (−)-**9b**·HCl (80% yield, 57% e.e.) was obtained. The analytical sample of (−)-**9b**·HCl (>99% e.e.) was obtained in only one crystallization from methanol/ethyl acetate from a sample of (−)-**9b**·HCl (22% e.e), obtained from a ketone (+)-**4b** (<30% e.e.). As can be seen from these data, partial epimerization of the starting ketones took place during the Friedländer reaction, which must be due to the acid reaction conditions, a fact that had been previously observed during the HCl-hydrolysis of ketals (+)- and (−)-**8b**. The Friedländer reaction of ketone (+)-**4b** with 2-aminobenzonitrile catalyzed by $ZnCl_2$ in nitrobenzene at 120°C showed a similar degree of epimerization.

Although we had succeeded in obtaining pure samples of (+)- and (−)-**9b**, in order to make more easily available these and related compounds, we tried the separation of the racemic mixture *rac*-**9b** by several procedures. Several attempts to selectively crystallize one or the other enantiomer from a methanol/ethyl acetate solution of the racemic mixture, by inducing the crystallization by addition of crystals of one of the enantiomers were fruitless. An attempt to separate *rac*-**9a** by column chromatography using the chiral stationary phase cellulose tris(3,5-dimethylphenyl)carbamate supported on silica gel (SDS 40, 40–60 μm), following the procedure described by Matlin et al.[25] was also fruitless. Also, several attempts to carry out the separation of *rac*-**9a** by crystallization of the salts derived from several

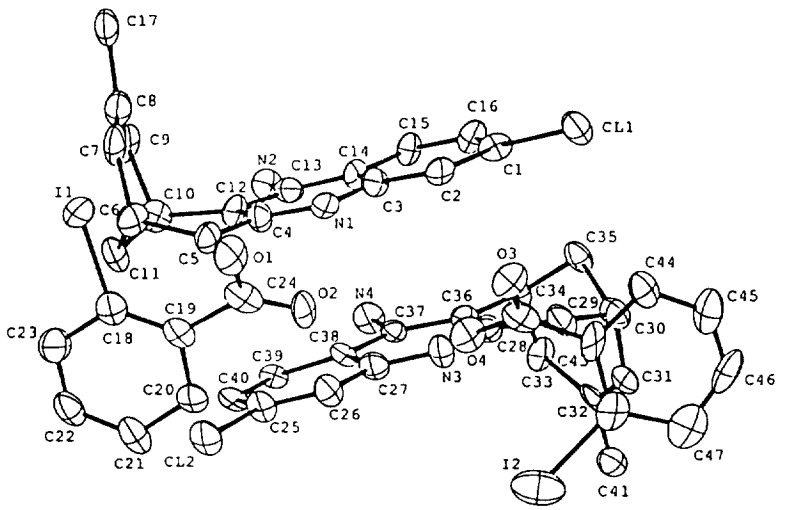


Fig. 1. Perspective drawing (ORTEP) of (−)-**10a** *o*-iodobenzoic acid salt. The numbering is that used for the X-ray analysis; selected distances [Å]: C7–C8 1.31(2), C8–C9 1.44(2)

enantiopure acids, such as (+)-camphorsulfonic and (+)-tartaric acid as well as (*S*)-naproxen in different solvents, gave products from which the liberated bases **9a** showed very low specific rotations. The best result was obtained by using (+)-camphorsulfonic acid in an isopropanol/water mixture: $[\alpha]_D^{20}=-5.3$ (c=1.00, methanol) for the liberated **9a**. Fortunately, we were able to separate efficiently *rac*-**9b** on a preparative scale (100–200 mg) by medium pressure liquid chromatography using microcrystalline cellulose triacetate (15–25 μm) as the chiral stationary phase and 96% ethanol as the eluent. The chromatographic fractions were analyzed by chiral HPLC, combined conveniently, transformed into the corresponding hydrochlorides and crystallized, which allowed us to obtain both enantiomers on an adequate scale (>100 mg) for the pharmacological tests.

The same procedure could then be successfully applied to the separation of other racemic compounds of this series, such as *rac*-**9a**[2] and *rac*-**10a**. The latter is a new compound which was prepared in a standard way[2] by reaction of *rac*-**4a** with commercially available 2-amino-4-chlorobenzonitrile.

After much experimentation we were able to obtain a monocrystal of (−)-**10a** as a salt with *o*-iodobenzoic acid, whose X-ray diffraction analysis at low temperature (223 K) revealed its absolute configuration (Fig. 1).

It seems reasonable that (−)-**9a** and (−)-**9b** with the same sign and close values for their specific rotations to that of (−)-**10a** all have the same absolute configuration and vice versa for their enantiomers.

In conclusion, quite enantioselective syntheses of ketones (+)- and (−)-**4b** have been developed whose key-step consist of the enantioselective deprotonation of the prochiral ketone **5** followed by trapping of the enolate with N-phenyltriflimide. Friedländer condensation of these ketones with 2-aminobenzonitrile catalyzed by $AlCl_3$ or $ZnCl_2$ gave the corresponding aminoquinolines (−)- and (+)-**9b**, respectively, with partial epimerization. Racemic mixtures *rac*-**9a**, *rac*-**9b** and *rac*-**10a** have been separated on a preparative scale, which allowed the isolation of samples (>100 mg) of their enantiomers. The absolute configuration of these compounds has been obtained through the X-ray diffraction analysis of the (−)-**10a** *o*-iodobenzoic acid salt. The pharmacological study of these compounds is under way and will be published elsewhere.

3. Experimental

Melting points were determined on an MFB 595010 M Gallenkamp melting point apparatus. ^{1}H NMR spectra (500 MHz) were performed on a Varian VXR 500 spectrometer, while 300 MHz ^{1}H and 75.4 MHz ^{13}C NMR spectra were performed on a Varian Gemini 300. Except where otherwise stated, ^{1}H NMR spectra were recorded at 500 MHz and ^{13}C NMR spectra at 75.4 MHz in $CDCl_3$. Chemical shifts (δ) are reported in ppm related to internal tetramethylsilane. IR spectra were recorded on an FT-IR Perkin–Elmer spectrometer, model 1600. Optical rotations were measured on a Perkin–Elmer, model 241 polarimeter. Silica gel SDS 60 (60–200 μm) was used for the column chromatography. Chiral HPLC analyses were performed on a Waters model 600 liquid chromatograph provided with a variable λ detector, Waters model 486, using a Chiralcel OD-H column (25×0.46 cm) containing the chiral stationary phase cellulose tris(3,5-dimethylphenylcarbamate). Conditions A: mixture of hexane:isopropanol (99:1) as eluent, flow 0.45 mL/min, λ=215 nm. Conditions B: mixture of hexane:ethanol:diethylamine (70:30:0.1) as eluent, flow 0.2 mL/min, λ=235 nm. Conditions C: mixture of hexane:ethanol:diethylamine (75:25:0.1) as eluent, flow 0.3 mL/min, λ=235 nm. Solvents were of analytical grade. GC analyses were carried out on a Perkin–Elmer model 8600 gas–liquid chromatograph provided with an ionization flame detector, using for the stereospecific analyses a Supelco BETA-DEX 110® column (30 m×0.25 mm)) containing the chiral stationary phase β-cyclodextrin; pressure: 18 psi; injector temperature 250°C; detector temperature: 300°C. Conditions D: initial temperature: 75°C (for 2 min), heating rate: 1°C/min (for 10 min) and 0.5°C/min (for 20 min), final temperature: 95°C (for 175 min). Conditions E: initial temperature: 75°C (for 2 min), heating rate: 1°C/min (for 40 min), final temperature: 115°C (for 35 min). Chiral medium pressure liquid chromatography (MPLC) separation was carried out on equipment which consisted of a pump (Buchi 688), a variable λ UV detector (Buchi) and a column (25×2.5 cm) containing microcrystalline cellulose triacetate (15–25 μm) as the chiral stationary phase. Elemental analyses were carried out at the Microanalysis Service of the Centro de Investigación y Desarrollo (C.I.D.), Barcelona, Spain.

*3.1. 3-Methyl-2-oxaadamantan-1-ol, **1**, by reaction of **2** with LDA*

To a stirred solution of LDA (6.7 mL of a 2 M solution in heptane/THF/ethylbenzene, 13.4 mmol) at 0°C under argon, a solution of **2** (1.10 g, 4.47 mmol) in dry THF (60 mL) was added dropwise, and the mixture was stirred at room temperature for 5 h. A saturated aqueous solution of NH_4Cl (30 mL) and water (30 mL) were added and the mixture was extracted with diethyl ether (3×30 mL). The combined organic phases were washed with brine (30 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give **1** (700 mg, 94% yield), whose spectroscopic data coincide with those of an authentic sample.[1]

3.2. Attempted kinetic resolution of rac-***4a*** *by Sharpless enantioselective bihydroxylation*[8,9]

To a well-stirred mixture of *tert*-butanol (5 mL), water (5 mL), AD-mix-α (1.4 g) and methanesulfonamide (285 mg, 3.00 mmol), *rac*-**4a** (150 mg, 1.00 mmol) was added, and the mixture was stirred at room temperature for 72 h. Sodium sulfite (1.50 g, 11.9 mmol) was added and the mixture was stirred for 30 min. Water (20 mL) was added and the mixture was extracted with CH_2Cl_2 (5×20 mL). The combined organic phases were washed with aqueous 2 N KOH (2×10 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give a residue (160 mg) which was submitted to column chromatography (silica gel, 15 g). On elution with hexane:ethyl acetate (95:5), (−)-**4a** [90 mg, $[\alpha]_D^{20}=-5.7$ (c=1.00, CH_2Cl_2)] was obtained.

The low e.e. of this product could not be quantified by chiral GC (conditions E) due to insufficient resolution of the enantiomers. For the specific rotation of (−)-**4b**, see later on.

3.3. *Attempted kinetic resolution of* rac-***4a*** *by Jacobsen enantioselective epoxidation*[11,12]

To a cold (ice–water bath) solution of *rac*-**4a** (300 mg, 2.0 mmol), 4-phenylpyridine N-oxide (110 mg, 0.64 mmol) in CH_2Cl_2 (1.5 mL), (*R,R*)-(−)-N,N′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride (110 mg, 0.17 mmol) and a cold buffer solution (pH=11.3) of sodium hypochlorite (9.5 mL) were added, and the mixture was stirred at 0°C for 12 h. The reaction mixture was extracted with diethyl ether (30 mL) and CH_2Cl_2 (3×10 mL). The combined organic phases were filtered through a pad of Celite®, washed with water (2×25 mL) and brine (2×25 mL), dried (Na_2SO_2) and concentrated *in vacuo* to give a black oily residue which was submitted to column chromatography (silica gel, 11 g). On elution with hexane:ethyl acetate (95:5), (−)-**4a** [150 mg, $[\alpha]_D^{20}=-14.1$ (c=1.00, CH_2Cl_2)] was obtained.

3.4. rac-*7,7-Ethylenedioxy-3-trifluoromethanesulfonyloxybicyclo[3.3.1]non-2-ene,* rac-*7*

To a stirred solution of **5** (1.00 g, 5.1 mmol) in dry THF (36 mL) under argon at −78°C, a solution of LDA (2.8 mL of a 2 M solution in heptane/THF/ethylbenzene, 5.6 mmol) was added dropwise. After 10 min, N-phenyltriflimide (1.91 g, 5.35 mmol) was added at once, the mixture was allowed to warm to room temperature and stirred for 20 h at this temperature. The solvent was eliminated *in vacuo* and the residue was dissolved in ethyl acetate (50 mL) and washed with water (50 mL), 2 N NaOH (2×10 mL) and water (10 mL). The solution was dried (Na_2SO_4) and concentrated *in vacuo* and the residue was submitted to column chromatography (silica gel, 65 g, hexane/ethyl acetate mixtures) giving rise to *rac*-**7** (1.28 g, 77% yield) as an almost colourless oil, b.p. 55°C (0.5 torr). IR (KBr), ν: 2928, 2878, 1414, 1244, 1143, 1087, 1068, 1037, 1012, 978, 964, 875 cm^{-1}. ^1H NMR, δ: 1.61 (dt, J=12.5 Hz, J′=3.0 Hz, 1H, 9-H_{anti}), 1.72 (dtt, J=12.5 Hz, J′=3.0 Hz, J″=1.5 Hz, 1H, 9-H_{syn}), 1.77 (dd, J=14.0 Hz, J′=4.5 Hz, 1H, 8-H_α), 1.80–1.85 (comp. signal, 3H, 6-H_α, 6-H_β and 8-H_β), 2.27 (d, J=17.5 Hz, 1H, 4-H_β), 2.43 (m, 1H, 5-H), 2.57 (dd, J=17.5 Hz, J′=7.5 Hz, 1H, 4-H_α), 2.65 (broad s, 1H, 1-H), 3.78 (m, 2H) and 3.94 (m, 2H) (O–CH_2–CH_2–O), 5.76 (d, J=6.5 Hz, 1H, 2-H). ^{13}C NMR, δ: 28.2 (CH, C5), 29.2 (CH, C1), 30.0 (CH_2, C9), 33.3 (CH_2, C4), 38.0 (CH_2, C8), 41.5 (CH_2, C6), 63.1 (CH_2) and 64.8 (CH_2) (O–CH_2–CH_2–O), 107.7 (C, C7), 118.5 (C, q, J=320 Hz, OSO_2CF_3), 120.9 (CH, C2), 149.8 (C, C3). $C_{12}H_{15}F_3O_5S$ (328.30) calcd: C 43.90%, H 4.61%, S 9.77%, F 17.36%. Found: C 43.86%, H 4.59%, S 9.78%, F 17.02%.

3.5. rac-*7,7-Ethylenedioxy-3-ethylbicyclo[3.3.1]non-2-ene,* rac-***8b***

To a stirred suspension of $Me_2S{\cdot}CuBr$ complex (514 mg, 2.5 mmol) in dry THF (2 mL) under argon at −78°C, a solution of ethylmagnesium bromide (4.5 mL of a 1 M solution in THF, 4.5 mmol) was added dropwise. After removing the cooling bath, the grey suspension became black in 10–15 min. This suspension was then cooled again to −78°C, a solution of *rac*-**7** (164 mg, 0.5 mmol) in dry THF (2 mL) was added dropwise and the mixture was stirred at room temperature for 16 h. The reaction mixture was poured onto a saturated aqueous solution of NH_4Cl (20 mL), the organic phase was separated and the aqueous phase extracted with ethyl acetate (3×5 mL). The combined organic phases were washed with aqueous 10% $NaHCO_3$ (5 mL) and brine (5 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give an oily residue (110 mg) containing a mixture of *rac*-**8b** and *rac*-**7** in an approximate molar ratio of 7:1.

Column chromatography of this mixture (silica gel, 17 g, hexane/ethyl acetate mixtures) gave *rac*-**8b** (60 mg, 58% yield) as a yellowish oil, b.p. 60°C/0.5 torr. IR ($CHCl_3$), ν: 2962, 2925, 1452, 1427, 1364, 1246, 1227, 1215, 1190, 1143, 1085, 1022, 950, 856 cm^{-1}. ^1H NMR, δ: 0.97 (t, J=7.5 Hz, 3H, 3-CH_2–CH_3), 1.55 (broad d, J=12.0 Hz, 1H, 9-H_{anti}), 1.65 (broad d, J=12.0 Hz, 1H, 9-H_{syn}), 1.73 (compl. signal, 2H, 8-H_α and 8-H_β), 1.76 (compl. signal, 2H, 6-H_α and 6-H_β), 1.88 (d, J=17.0 Hz, 1H, 4-H_β), 1.93 (m, 2H, 3-CH_2–CH_3), 2.21 (comp. signal, 1H, 4-H_α), 2.23 (broad s, 1H, 5-H), 2.38 (broad s, 1H, 1-H), 3.71–3.97 (comp. signal, 4H, O–CH_2–CH_2–O), 5.44 (dm, J=6.5 Hz, 1H, 2-H). ^{13}C NMR, δ: 12.3 (CH_3, 3-CH_2–CH_3), 27.6 (CH, C5), 29.1 (CH, C1), 30.1 (CH_2, 3-CH_2–CH_3), 31.2 (CH_2, C9), 34.4 (CH_2, C4), 39.1 (CH_2, C8), 41.7 (CH_2, C6), 62.7 (CH_2) and 64.4 (CH_2) (O–CH_2–CH_2–O), 109.0 (C, C7), 122.6 (CH, C2), 139.6 (C, C3). $C_{13}H_{20}O_2$ (208.30) calcd: C 74.94%, H 9.68%. Found: C 74.83%, H 9.69%.

3.6. rac-*7-Ethylbicyclo[3.3.1]non-6-en-3-one*, rac-***4b***

A solution of *rac*-**8b** (72 mg, 0.35 mmol) in THF (1.12 mL) and 2 N HCl (1.12 mL) was stirred at room temperature for 6 h. The organic solvent was removed *in vacuo* without heating, the aqueous residue was diluted with water (1 mL) and extracted with CH_2Cl_2 (3×1 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* without heating to give *rac*-**4b** (36 mg, 64% yield) as a yellowish oil whose spectroscopic data coincide with those of an authentic sample.[1]

3.7. rac-*7,7-Ethylenedioxy-3-vinylbicyclo[3.3.1]non-2-ene*, rac-***8c***, *and* rac-*7-vinylbicyclo[3.3.1]non-6-en-3-one*, rac-***4c***

Procedure A. To a stirred suspension of anh. LiCl (260 mg, 6.1 mmol) and $Pd[P(C_6H_5)_3]_4$ (46 mg, 0.04 mmol) in anh. THF (4.8 mL), a solution of *rac*-**7** (656 mg, 2.0 mmol) and tributyl(vinyl)tin (0.58 mL, 2.0 mmol) in anh. THF (4.8 mL) was added and the mixture was heated under reflux for 20 h. The mixture was allowed to cool to room temperature, diluted with pentane (20 mL) and washed with water (10 mL), 10% aqueous ammonia (10 mL) and brine (10 mL). The dried organic phase (Na_2SO_4) was concentrated *in vacuo* to give a yellow oil (846 mg) which was submitted to column chromatography (silica gel, 75 g, hexane/ethyl acetate mixtures) yielding *rac*-**8c** (209 mg, 51% yield) and *rac*-**4c** slightly contaminated with *rac*-**8c** (27 mg, 8% approx. yield).

Procedure B. This reaction was carried out as before, starting from the same amount of reagents. The crude yellow oil (949 mg) was introduced onto the silica gel column as before and it was kept on the column for 16 h before elution was started. In this way, *rac*-**8c** (35 mg, 9% yield) and *rac*-**4c** (195 mg, 60% yield) were obtained.

3.7.1. *Spectroscopic data of* rac-***8c***

^1H NMR (300 MHz), δ: 1.62 (broad d, J=12.3 Hz, 1H, 9-H_{anti}), 1.71 (broad d, J=12.3 Hz, 1H, 9-H_{syn}), 1.72–1.91 (compl. signal, 4H, 6-H_α, 6-H_β, 8-H_α and 8-H_β), 2.14 (d, J=16.5 Hz, 1H, 4-H_β), 2.39 (broad s, 1H, 5-H), 2.43 (m, 1H, 4-H_α), 2.55 (broad s, 1H, 1-H), 3.70–3.97 (compl. signal, 4H, O–CH_2–CH_2–O), 4.90 (d, J=10.7 Hz, 1H, vinyl 2-H_{trans}), 5.05 (d, J=17.5 Hz, 1H, vinyl 2-H_{cis}), 5.84 (broad d, J=6.4 Hz, 1H, 2-H), 6.39 (dd, J=17.5 Hz, J′=10.7 Hz, 1H, vinyl 1-H). ^{13}C NMR, δ: 26.9 (CH, C5), 29.5 (CH, C1), 30.1 (CH_2) and 31.0 (CH_2) (C4 and C9), 38.7 (CH_2, C8), 41.6 (CH_2, C6), 62.6 (CH_2) and 64.6 (CH_2) (O–CH_2–CH_2–O), 108.4 (C, C7), 109.7 (CH_2, vinyl C2), 132.3 (CH, C2), 135.9 (C, C3), 139.6 (CH, vinyl C1).

3.7.2. Analytical and spectroscopic data of rac-***4c***

M.p. 61–63°C (sublimed). IR (KBr), ν: 3084, 3021, 2993, 2925, 2857, 1702, 1634, 1594, 1446, 1424, 1413, 1361, 1341, 1318, 1287, 1276, 1227, 1209, 1183, 1166, 1092, 1050, 998, 915, 906, 872, 804 cm^{-1}. ^1H NMR, δ: 1.97 (dm, J=12.5 Hz, 1H, 9-H_{anti}), 2.02 (dm, J=12.5 Hz, 1H, 9-H_{syn}), 2.12 (d, J=17.5 Hz, 1H, 8-Hβ), 2.28 (dq, J=15.5 Hz, J′=2.0 Hz, 1H, 2-Hβ), 2.34 (dq, J=14.5 Hz, J′=2.0 Hz, 1H, 4-Hβ), 2.45 (dd, J=17.5 Hz, J′=6.5 Hz, 1H, 8-Hα), 2.47 (dd, J=14.5 Hz, J′=4.5 Hz, 1H, 4-Hα), 2.51 (dd, J=15.5 Hz, J′=6.5 Hz, 1H, 2-Hα), 2.67 (broad m, 1H, 1-H), 2.79 (broad m, 1H, 5-H), 4.91 (d, J=11.0 Hz, 1H, vinyl 2-H_{trans}), 5.03 (d, J=17.5 Hz, 1H, vinyl 2-H_{cis}), 5.74 (broad d, J=6.0 Hz, 1H, 6-H), 6.24 (dd, J=17.5 Hz, J′=11.0 Hz, 1H, vinyl 1-H). ^{13}C NMR, δ: 29.5 (CH, C1), 30.4 (CH_2, C9), 31.2 (CH_2, C8), 31.4 (CH, C5), 46.1 (CH_2, C4), 48.9 (CH_2, C2), 111.6 (CH_2, vinyl C2), 131.7 (CH, C6), 134.1 (C, C7), 139.0 (CH, vinyl C1), 211.4 (C, C3). $C_{11}H_{14}O$ (162.23) calcd: C 81.43%, H 8.70%. Found: C 81.41%, H 8.66%.

3.8. (+)-(1S,5S)-7,7-Ethylenedioxy-3-trifluoromethanesulfonyloxybicyclo[3.3.1]non-2-ene, (+)-7

A stirred solution of (−)-bis[(*S*)-1-phenylethyl]amine [2.07 g, 9.2 mmol, $[\alpha]_D^{20}=-167$ (c=1.02, $CHCl_3$)] in dry THF (80 mL) was cooled to −78°C. A solution of *n*-BuLi (5.74 mL, 1.6 M solution in hexane, 9.18 mmol) was added dropwise over 5 min. The solution was allowed to warm to room temperature over 1 h and then it was cooled again to −78°C. A solution of LiCl (65 mg, 1.5 mmol) in dry THF (7 mL) and then a solution of **5** (1.50 g, 7.65 mmol) in dry THF (9 mL) were added dropwise. The mixture was stirred at −78°C for 15 min and then a solution of N-phenyltriflimide (4.10 g, 11.5 mmol) in dry THF (8 mL) was added dropwise over 10 min. The reaction mixture was allowed to warm to room temperature and stirred for 16 h. Most of the organic solvent was eliminated *in vacuo* (final approximate volume: 8 mL) and ethyl acetate (8 mL), hexane (165 mL) and water (40 mL) were added to the residue. The aqueous phase was separated and the organic phase was washed with aqueous 2 N NaOH (2×40 mL), 2 N HCl (2×40 mL) and water (2×50 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give a residue (3.23 g) consisting of a mixture of a white solid and a yellowish oil. Column chromatography of this residue (silica gel, 140 g, hexane/ethyl acetate mixtures) gave (+)-**7** (1.99 g, 79% yield) as a yellowish oil, b.p. 65°C/1 torr, $[\alpha]_D^{20}=+43$ (c=1.08, $CHCl_3$), 81% e.e. by chiral HPLC under conditions A [(+)-**7**, r.t. 16.04 min, $k'_1=1.34$, (−)-**7**, r.t. 16.98 min, $k'_2=1.47$, α=1.10, res=1.47]. $C_{12}H_{15}F_3O_5S$ (328.30) calcd: C 43.90%, H 4.61%, S 9.77%. Found: C 43.49%, H 4.52%, S 9.76%. The NMR and IR data coincide with those of *rac*-**7**.

*3.9. (+)-(1S,5S)-7,7-Ethylenedioxy-3-ethylbicyclo[3.3.1]non-2-ene, (+)-**8b***

From (+)-**7** (1.50 g, 4.57 mmol, 79% e.e.) and following the same procedure described above for the preparation of *rac*-**8b**, (+)-**8b** (687 mg, 72% yield) was obtained as a yellowish oil. The analytical sample was obtained by distillation, b.p. 60°C/0.5 torr, $[\alpha]_D^{20}=+87.2$ (c=1.03, $CHCl_3$), 77% e.e. by chiral GC under conditions D [(+)-**8b**, r.t. 186.33 min, (−)-**8b**, r.t. 183.04 min]. $C_{13}H_{20}O_2$ (208.30) calcd: C 74.94%, H 9.68%. Found: C 74.97%, H 9.67%.

*3.10. (+)-(1S,5S)-7-Ethylbicyclo[3.3.1]non-6-en-3-one, (+)-**4b***

To a solution of (+)-**8b** (530 mg, 2.55 mmol, 77% e.e.) in CH_2Cl_2 (15 mL), silica gel (SDS 40, 40–60 μm, 6.5 g) was added and the suspension was stirred at room temperature for 27 h. The solvent was removed *in vacuo* and the residue was submitted to column chromatography (silica gel, 15 g, hexane:ethyl acetate=97:3) to give (+)-**4b** (340 mg, 81% yield) as a yellowish oil, b.p. 45°C/0.4 torr, $[\alpha]_D^{20}=+81$

(c=0.96, $CHCl_3$), 77% e.e. by chiral GC under conditions E [(+)-**4b**, r.t. 70.37 min, (−)-**4b**, r.t. 71.52 min]. $C_{11}H_{16}O$ (164.25) calcd: C 80.43%, H 9.83%. Found: C 80.30%, H 9.74%.

*3.11. (−)-(7S,11S)-12-Amino-9-ethyl-6,7,10,11-tetrahydro-7-11-methanocyclooctenо[b]quinoline, (−)-**9b***

Procedure A: To a suspension of anhydrous $AlCl_3$ (252 mg, 1.89 mmol) and 2-aminobenzonitrile (168 mg, 1.42 mmol) in 1,2-dichloroethane (7 mL), a solution of (+)-**4b** (155 mg, 0.94 mmol, 77% e.e.) in 1,2-dichloroethane (1.5 mL) was added dropwise and the mixture was stirred under reflux for 14 h. The reaction mixture was allowed to cool to room temperature, water (6 mL) and THF (6 mL) were added, the mixture was made basic by addition of aqueous 5 N NaOH (2.5 mL) and stirred at room temperature for 30 min. The organic solvents were removed under reduced pressure and the residue, consisting of an aqueous phase and a gummy brown solid, was filtered. The solid was dissolved in methanol (10 mL) and the solvent was removed *in vacuo*. The waxy orange residue (340 mg) thus obtained was submitted to column chromatography (silica gel, 65 g, hexane/ethyl acetate/methanol mixtures) to give (−)-**9b** (199 mg, 80% yield, 57% e.e. by chiral HPLC under conditions B [(−)-**9b**, r.t. 18.40 min, k'_1=0.17; (+)-**9b**, r.t. 20.46 min, k'_2=0.31, α=1.82, res. 1.58]. The above product was dissolved in methanol (4 mL), 0.38 N HCl in diethyl ether (7 mL) was added and the solvent was removed *in vacuo* to give (−)-**9b**·HCl (236 mg), from which it was not possible to obtain a crystalline product.

On crystallisation of a sample of (−)-**9b**·HCl [242 mg, 22% e.e., from another run] from a mixture of methanol (2 mL) and ethyl acetate (5 mL), a pure sample of (−)-**9b**·HCl [$[\alpha]_D^{20}$=−345 (c=0.99, methanol), >99% e.e., established on the free base by chiral HPLC], m.p. 250°C (dec.), was obtained. IR (KBr), ν: 3550–2500 (max. at 3329, 3180, 2930, 2880 and 2821), 1667, 1650, 1639, 1607, 1585, 1544, 1496, 1461, 1412, 1373, 1239, 1211, 762 cm^{-1}. $C_{18}H_{21}N_2Cl \cdot 2/3H_2O$ (312.83) calcd: C 69.10%, H 7.20%, N 8.95%, Cl 11.33%. Found: C 69.16%, H 6.91%, N 8.88%. The NMR data coincide with those of *rac*-**9b**.[2]

Procedure B: A suspension of (+)-**4b** [200 mg, 1.22 mmol, $[\alpha]_D^{20}$=+75 (c=1.00, $CHCl_3$)], 2-aminobenzonitrile (144 mg, 1.22 mmol) and anhydrous $ZnCl_2$ (250 mg, 1.83 mmol) in nitrobenzene (3.5 mL) was stirred at 120°C for 2 h. The reaction mixture was cooled with an ice–water bath, made basic with aqueous 5 N NaOH (5 mL) and the nitrobenzene was azeotropically distilled off with water. The suspension was allowed to cool to room temperature and filtered. The light brown waxy solid was washed with water (20 mL) and dissolved in methanol (50 mL). The solvent was removed *in vacuo* and the residue (196 mg) was submitted to column chromatography (silica gel, 40 g, hexane/ethyl acetate/methanol mixtures as eluent) to give (−)-**9b** (118 mg, 37% yield, 56% e.e. by chiral HPLC) as a light orange solid.

3.12. (−)-(1R,5R)-7,7-Ethylenedioxy-3-trifluoromethanesulfonyloxybicyclo[3.3.1]non-2-ene, (−)-7

(−)-**7** was obtained following the same procedure previously described for the preparation of (+)-**7**, by using (+)-bis[(*R*)-1-phenylethyl]amine [$[\alpha]_D^{20}$=+165 (c=1.10, $CHCl_3$)]. From **5** (2.0 g, 10.2 mmol), (−)-**7** (2.15 g, 64% yield) was obtained as a yellowish oil, b.p. 65°C/1 torr, $[\alpha]_D^{20}$=−45.6 (c=1.02, $CHCl_3$), 81% e.e. by chiral HPLC. $C_{12}H_{15}F_3O_5S$ (328.30) calcd: C 43.90%, H 4.61%, S 9.77%. Found: C 43.97%, H 4.61%, S 9.87%. The spectroscopic data (IR and NMR) coincide with those of *rac*- and (+)-**7**.

3.13. (−)-(1R,5R)-7,7-Ethylenedioxy-3-ethylbicyclo[3.3.1]non-2-ene, (−)-8b

From (−)-**7** (115 mg, 0.35 mmol, 81% e.e.), following the same procedure described above for the preparation of (+)-**8b**, (−)-**8b** (49 mg, 67% yield) was obtained as a yellowish oil, b.p. 60°C/0.5 torr, $[\alpha]_D^{20}=-88.6$ (c=1.03, $CHCl_3$), 81% e.e. by chiral GC. $C_{13}H_{20}O_2$ (208.30) calcd: C 74.94%, H 9.68%. Found: C 74.84%, H 9.69%. Its spectroscopic data (IR and NMR) coincide with those of *rac*- and (+)-**8b**.

3.14. (−)-(1R,5R)-7-Ethylbicyclo[3.3.1]non-6-en-3-one, (−)-4b

From (−)-**7** (1.50 g, 4.57 mmol, 81% e.e.), following the same procedure previously described for the preparation of (+)-**8b**, impure (−)-**8b** was obtained, a part of which was hydrolyzed as before to give, after column chromatography, pure (−)-**4b** (179 mg, 30% global yield) as a yellowish oil, b.p. 45°C/0.4 torr, $[\alpha]_D^{20}=-85$ (c=0.93, $CHCl_3$), 81% e.e. by chiral GC. $C_{11}H_{16}O$ (164.25) calcd: C 80.43%, H 9.83%. Found: C 80.33%, H 9.84%. The spectroscopic data (IR and NMR) coincide with those of *rac*- and (+)-**4b**.[1] In another run, from (−)-**7** (79% e.e.), (−)-**4b** was obtained in 69% global yield.

3.15. (+)-(7R,11R)-12-Amino-9-ethyl-6,7,10,11-tetrahydro-7-11-methanocycloocteno[b]quinoline, (+)-9b

Starting from (−)-**4b** [400 mg, 2.44 mmol, obtained as before from a sample of (−)-**7**, 79% e.e.] and following the same procedure described above for the preparation of (−)-**9b**, (+)-**9b** (480 mg, 75% yield, 53% e.e. by chiral HPLC) was obtained. It was transformed as before into its hydrochloride, (−)-**9b**·HCl (544 mg) which on crystallization from a mixture of ethyl acetate (5 mL) and methanol (2.5 mL), gave (−)-**9b**·HCl (188 mg, $[\alpha]_D^{20}=+353$ (c=0.95, methanol), 99% e.e. by chiral HPLC), m.p. 225°C (dec.). IR (KBr), ν: 3550–2450 (max. at 3328, 3178, 2890 and 2819), 1667, 1650, 1585, 1496, 1464, 1412, 1373, 1184, 1158, 852, 769 cm^{-1}. $C_{18}H_{21}N_2Cl$ (300.83) calcd: C 71.86%, H 7.04%, N 9.31%. Found: C 71.77%, H 7.00%, N 9.26%. The NMR data coincide with those of *rac*-**9b**.[2]

3.16. rac-12-Amino-3-chloro-6,7,10,11-tetrahydro-9-methyl-7-11-methanocycloocteno[b]quinoline, rac-10a

To a suspension of anhydrous $AlCl_3$ (2.13 g, 16.0 mmol) and 2-amino-4-chlorobenzonitrile (2.5 g, 16.4 mmol) in 1,2-dichloroethane (20 mL), a solution of *rac*-**4a** (1.60 g, 10.7 mmol) in 1,2-dichloroethane (20 mL) was added dropwise and the reaction mixture was heated under reflux for 7 h. The mixture was allowed to cool to room temperature, water (60 mL) and THF (70 mL) were added, the mixture was made basic by addition of aqueous 5 N NaOH and then it was stirred at room temperature for 30 min. The organic solvents were removed *in vacuo* and the remaining aqueous mixture was filtered to separate a gummy brown solid (4.06 g) which was submitted to column chromatography (silica gel, 65 g, hexane/ethyl acetate/methanol mixtures) to give *rac*-**10a** (2.00 g, 66% yield) as a waxy material.

A part of the above product (980 mg, 3.44 mmol) was dissolved in a mixture of methanol (20 mL) and $CHCl_3$ (20 mL). An excess of 0.38 N HCl in diethyl ether (18 mL, 6.84 mmol) was added and the solvents were removed *in vacuo* to give *rac*-**10a**·HCl (1.23 g) which on crystallization from a mixture of ethyl acetate (30 mL) and methanol (20 mL) gave pure *rac*-**10a**·HCl (980 mg, 55% yield from *rac*-**4a**), m.p. 250.5–252.5°C. IR (KBr), ν: 3700–2350 (max. at 3337, 3145, 2924, 2825 and 2700), 1661, 1636, 1589, 1490, 1471, 1415, 1371, 1260, 1235, 1182, 1084, 1020, 946, 926, 825, 770 cm^{-1}. ^1H NMR (CD_3OD), δ: 1.57 (s, 3H, 9-CH_3), 1.95 (dm, J=12.5 Hz, 1H, 13-H_{syn}), 1.97 (d, J=18.0 Hz, 1H, 10-H_β),

2.06 (dm, J=12.5 Hz, 1H, 13-H_{anti}), 2.51 (broad dd, J=18.0, J′=5.5 Hz, 1H, 10-H_{α}), 2.77 (broad s, 1H, 7-H), 2.88 (dt, J=18.0 Hz, J′=2.0 Hz, 6-H_{β}), 3.20 (dd, J=18.0 Hz, J′=5.5 Hz, 1H, 6-H_{α}), 3.37 (broad m, 1H, 11-H), 4.83 (broad s, NH_2+NH^++H_2O), 5.57 (broad d, J=5.5 Hz, 1H, 8-H), 7.55 (dd, J=9.0 Hz, J′=2.0 Hz, 1H, 2-H), 7.75 (d, J=2.0 Hz, 1H, 4-H), 8.35 (d, J=9.0 Hz, 1H, 1-H). ^{13}C NMR (CD_3OD), δ: 23.5 (CH_3, 9-CH_3), 27.5 (CH, C11), 28.1 (CH, C7), 29.2 (CH_2, C13), 35.8 (CH_2) and 35.9 (CH_2) (C6 and C10), 115.2 (C) and 115.5 (C) (C11a and C12a), 119.1 (CH, C4), 125.1 (CH, C8), 126.4 (CH, C1), 127.6 (CH, C2), 134.9 (C, C9), 139.4 (C, C4a), 140.3 (C, C3), 153.0 (C, C5a), 156.6 (C, C12). $C_{17}H_{17}N_2Cl \cdot HCl \cdot H_2O$ (339.27) calcd: C 60.18%, H 5.95%, N 8.26%, Cl 20.90%. Found: C 60.34%, H 5.88%, N 8.17%, Cl 20.94%.

3.17. *Preparative resolution of* rac-**9a** *by chiral medium pressure liquid chromatography (chiral MPLC)*

The chromatographic resolution of *rac*-**9a** was carried out by using an MPLC apparatus provided with a column containing microcrystalline cellulose triacetate (15–25 μm) as the chiral stationary phase. The sample of *rac*-**9a** (550 mg) was introduced as free base in 4 portions (1×100 mg+3×150 mg) using 96% ethanol (2 mL/min) as the only eluent and solvent. The chromatographic fractions (5 mL) were analyzed by chiral HPLC under conditions B [(−)-**9a**, r.t. 18.49 min, k'_1=0.18, (+)-**9a**, r.t. 20.53 min, k'_2=0.31 α=1.72, res.=1.93] and combined conveniently. In this way, (−)-**9a** (189 mg, >90% e.e.) and (+)-**9a** (140 mg, >80% e.e.) were obtained. The remaining product consisted of mixtures of both enantiomers with lower e.e.s.

A solution of (−)-**9a** (189 mg) in methanol (10 mL) was treated with excess 0.38 N HCl in diethyl ether (10 mL) and the organic solvents were eliminated *in vacuo*. The residue (264 mg) was dissolved in methanol (0.25 mL), ethyl acetate (1.5 mL) was added and the precipitated solid was filtered, to give (−)-**9a**·HCl (124 mg) as a pale yellow solid, m.p. 240°C (dec.), $([\alpha]_D^{20}$=−328 (c=1.00, methanol), 90% e.e. by chiral HPLC on the liberated base). IR (KBr), ν: 3550–2500 (max. at 3338, 3182, 2811), 1666, 1650, 1636, 1604, 1585, 1497, 1457, 1414, 1374, 765 cm^{-1}. $C_{17}H_{19}N_2Cl \cdot 1/2H_2O$ (295.81) calcd: C 69.02%, H 6.82%, N 9.47%, Cl 11.98%. Found: C 68.76%, H 6.60%, N 9.36%.

Similarly, from (+)-**9a** (140 mg), (+)-**9a**·HCl (114 mg) was obtained as a pale yellow solid, m.p. 250°C (dec.) $([\alpha]_D^{20}$=+309 (c=1.00, methanol), 87% e.e.). IR (KBr), ν: 3500–2500 (max. at 3319, 3178, 2809), 1666, 1649, 1638, 1607, 1495, 1457, 1414, 1373, 765 cm^{-1}. $C_{17}H_{19}N_2Cl \cdot 2/3H_2O$ (298.80) calcd: C 68.33%, H 6.86%, N 9.37%. Found: C 68.24%, H 6.68%, N 9.27%.

3.18. *Preparative resolution of* rac-**9b** *by chiral MPLC*

The resolution of *rac*-**9b** was carried out as described before for *rac*-**9a**. The sample (540 mg) was introduced in portions (4×135 mg) and after adequately combining the collected fractions, (−)-**9b** (269 mg, >90% e.e.) and (+)-**9b** (241 mg, >85% e.e.) were obtained. From (+)-**9b** (241 mg), crude (+)-**9b**·HCl (275 mg) was obtained which on crystallization from a mixture of methanol (1.8 mL) and ethyl acetate (2.5 mL) gave (+)-**9b**·HCl (85 mg) as a pale yellow solid, (>99% e.e., by chiral HPLC). Similarly, from (−)-**9b** (269 mg), (−)-**9b**·HCl (130 mg) was obtained as a pale yellow solid (>99% e.e.).

3.19. *Preparative resolution of* rac-**10a** *by chiral MPLC*

The resolution of *rac*-**10a** was carried out in a similar manner to that described for *rac*-**9a**. The sample was introduced in six portions (1×300 mg+1×150 mg+4×200 mg). In this case, in order to reduce the elution time of (+)-**10a**, once (−)-**10a** had been mostly eluted, the eluent was changed from ethanol to

methanol. The fractions were analyzed by chiral HPLC under conditions C [(−)-**10a**, r.t. 13.98 min, k'_1=0.35, (+)-**10a**, r.t. 15.69 min, k'_2=0.51, α=1.46, res.=2.16] and combined conveniently. A group of fractions with low e.e. were newly chromatographed and processed as before. Globally, (−)-**10a** (590 mg, 86% e.e.) and (+)-**10a** (690 mg, 87% e.e.) were obtained.

Compound (−)-**10a** (590 mg) was decolourized with active charcoal in methanol, transformed into the corresponding hydrochloride as usual and crystallized from a mixture of methanol (3 mL) and acetonitrile (10 mL) to give (−)-**10a**·HCl (220 mg) as a pale yellow solid, m.p. 229–230°C ($[\alpha]_D^{20}$=−261 (c=1.00, methanol), >99% e.e.). IR (KBr), ν: 3650–2400 (max. at 3333, 3178, 2927, 2810, 2679), 1657, 1633, 1586, 1489, 1465, 1411, 1370, 1184, 1084, 948, 928, 880, 827, 770 cm^{-1}. $C_{17}H_{17}N_2Cl \cdot HCl \cdot 5/4H_2O$ (343.77) calcd: C 59.39%, H 6.01%, N 8.15%. Found: C 59.68%, H 5.80%, N 8.25%.

Similarly, from (+)-**10a** (690 mg), (+)-**10a**·HCl (140 mg) was obtained as a pale yellow solid, m.p. 250–252°C ($[\alpha]_D^{20}$=+255 (c=1.00, methanol), 87% e.e.). IR (KBr), ν: 3650–2450 (max. at 3335, 3176, 2926, 2810, 2679), 1652, 1635, 1585, 1489, 1463, 1412, 1371, 1184, 1084, 948, 926, 879, 826, 770 cm^{-1}. $C_{17}H_{17}N_2Cl \cdot HCl \cdot 3/4H_2O$ (334.76) calcd: C 60.99%, H 5.88%, N 8.37%. Found: C 60.83%, H 5.85%, N 8.34%. The NMR spectra of (+)- and (−)-**10a**·HCl coincide with those of *rac*-**10a**.

3.20. *Preparation of (−)-**10a** o-iodobenzoic acid salt*

From (−)-**10a** (60 mg, 0.21 mmol), liberated from the above (−)-**10a**·HCl, the *o*-iodobenzoic acid salt was prepared by standard procedures. On slow crystallization (1 month) from isopropanol (12 mL), suitable crystals for X-ray diffraction analysis were obtained, which were kept under the solvent to avoid fragmentation on drying.

3.21. *X-Ray crystal-structure determinations of (−)-**10a** o-iodobenzoic acid salt*

A prismatic crystal was selected and mounted on an Enraf–Nonius CAD4 four-circle diffractometer. Unit cell parameters were determined by automatic centering of 25 reflections ($12<\theta<21°$) and refined by the least-squares method. Intensities were collected with graphite-monochromatized Mo-Kα radiation, using ω/2θ scan technique. 2959 reflections were measured in the range $1.40 \geq \theta \geq 29.97$, 2919 of which were non-equivalent by symmetry [R_{int} (on I)=0.016]. 1744 reflections were assumed as observed by applying the condition $I \geq 2\sigma(I)$. Three reflections were measured every two hours 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 the SHELXS computer program[26] and refined by the full-matrix least-squares method with the SHELX-93 computer program[27] using 2869 reflections (very negative intensities were not assumed). The function minimized was $\Sigma\, w[|F_o|^2-|F_c|^2]^2$, where $w=[\sigma^2(I)]^{-1}$, and $P=(|F_o|^2+2|F_c|^2)/3$. Values of f, f′ and f″ were taken from International Tables of X-Ray Crystallography.[28] The chirality of the structure was defined by the Flack coefficient, which is equal to 0.01(2) for the given results.[29] All H atoms were computed and refined with an overall isotropic temperature factor by using a riding model. Goodness of fit=0.933 for all observed reflections. Mean shift/e.s.d.=0.00. The results are shown in Table 1.

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Table 1
Experimental data of the X-ray crystal structure determination of (−)-**10a** *o*-iodobenzoic acid salt

Molecular formula	$C_{24}H_{22}ClIN_2O_2.1.5H_2O$	F(000)	562
Molecular mass	559.81	*d*(calcd) [Mg m^{-3}]	1.556
Temperature	223(2)K	Size of crystal [mm]	0.1 x 0.1 x 0.2
Crystal system	Triclinic	Measured reflections	2959
Space grup	P1	Independent reflections	2919
Cell parameters	[a]	Observed reflections	1744
a [Å]	7.949(5)	μ(Mo-*K*α) [mm^{-1}][b]	1.481
b [Å]	10.985(5)	*R*	0.0349
c [Å]	14.914(9)	*R*w	0.0401
α [°]	81.91(5)	Absolute structure parameter	0.01(2)
β [°]	78.93(5)	Diff. Four. $\Delta\rho_{max}$[c] (eÅ^{-3})	0.224
γ [°]	69.75 (4)	$\Delta\rho_{min}$[d] (eÅ^{-3})	-0.245
V [Å^3]	1195.2(12)	Refined parameters	569
Z	2	Max. shift / e.s.d.	0.00

[a] Determined by automatic centering of 25 reflections ($12 \leq \theta \leq 21°$). [b] μ(Mo-*K*α), Linear absorption coefficient. Radiation Mo-*K*α (λ = 0.71069Å). [c] Maximum and [d] minimum peaks in final difference synthesis.

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