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A Practical Enantioselective Synthesis of Epibatidine

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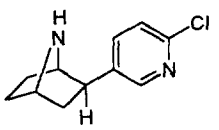
Abstract: Two different syntheses of Epibatidine (1) were designed and carried out using easily accessible reagents and convenient reaction conditions. The ring closure of the prochiral precursor **4** catalyzed by optically active α-phenyl-ethyl-amine gave the key intermediate **5** in over 80% ee from which the natural product (-)-**1** has been prepared. Copyright © 1996 Elsevier Science Ltd

Introduction

Epibatidine (**1**) was isolated from the skin extract of the Ecuadorian poison frog *Epipedobates tricolor* in 1992 by Daly *et al.* represents a new class of amphibian alkaloids. From biological investigations[1,2] it has been found that epibatidine possesses extremely interesting pharmacological properties. In particular, epibatidine is an analgesic, operating via a non-opioid mechanism, several hundred times more potent than morphine. The exciting biological properties of epibatidine combined with the unique structure aroused the interest of synthetic chemists. Since less than 0.5 mg of alkaloid was isolated from the skin extract of 750 frogs, further biological studies required synthetic material.



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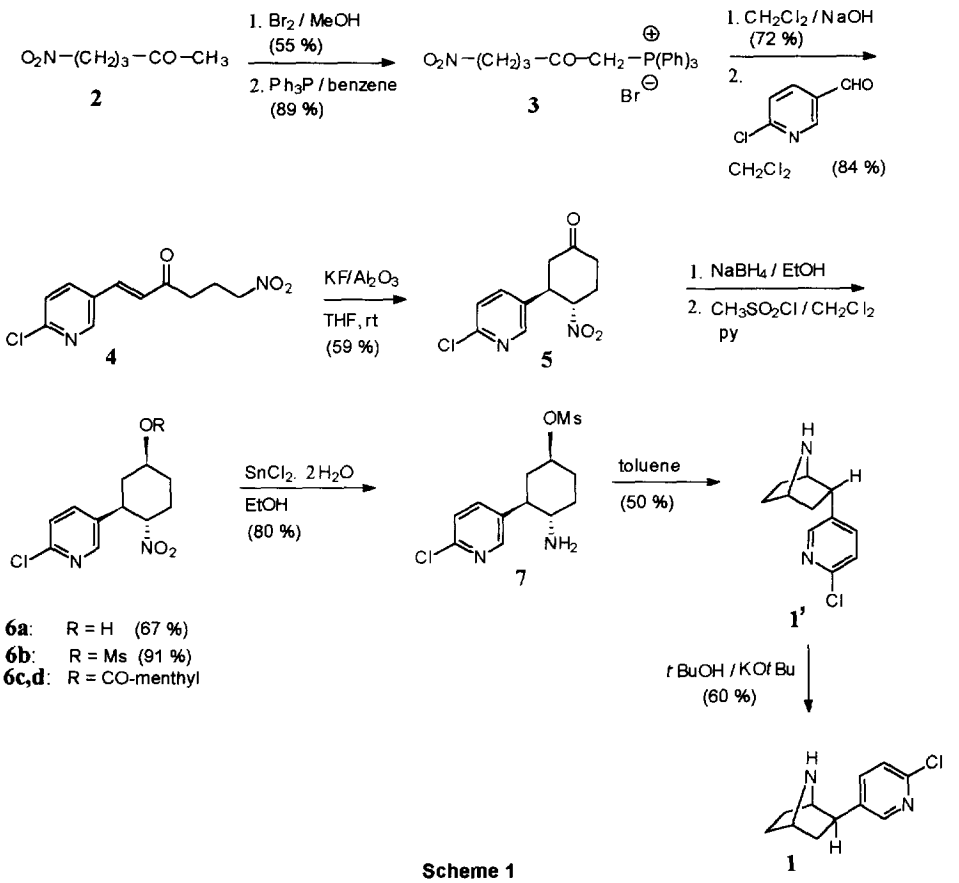
This need triggered an unprecedented competition among laboratories around the world, and in a relatively short time several synthetic approaches to the target compound were reported.[3]

The main goal of our synthetic strategy was to create a practical route to natural epibatidine (**1**) on a large scale to assist biological investigations. Thus we wanted to use commonly available starting materials and well known, and well controllable chemical transformations.

Results and Discussion

In a preliminary communication[3g] we reported our first approach to epibatidine (Scheme 1). Accordingly, nitromethane was allowed to react with methyl vinyl ketone to give compound **2**. After bromination and subsequent quaternarization with triphenylphosphine the salt **3** was obtained. Wittig reaction

of the appropriate phosphorane with chloropyridine aldehyde gave rise to **4**. Treatment of the latter compound with potassium fluoride/alumina furnished the cyclohexane derivative **5**. Later on it turned out that using simple potassium carbonate also does the job. Reduction of the keto group in **5** yielded with high stereoselectivity the corresponding alcohol **6a** (R=H) which was mesylated giving **6b** ($R=CH_3SO_2$). Subsequent reduction of the nitro group afforded amine **7**, which on boiling immediately in toluene resulted in the *endo* isomer of epibatidine (**1'**). On boiling the latter compound in *tert.* butanol in the presence of potassium *tert.*-butoxide epimerization occurred, and racemic epibatidine (**1**) was obtained. The resolution of **1** has already been described.[3b] The epimerization of the N/BOC derivative of **1** is also known.[3e,f] The detailed NMR characterization of epibatidine and its epimer was given in the preliminary communication.

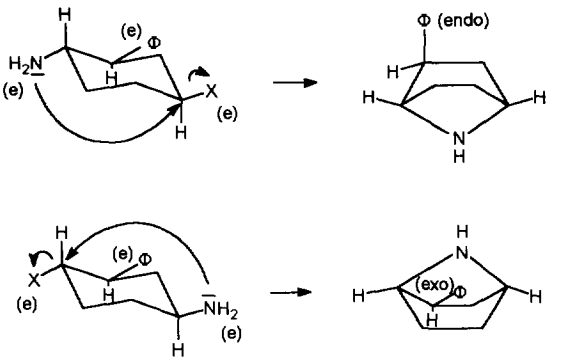


Scheme 1

To base our design on the epimerization in the last step was not without some sense of adventure, since 2-chloropyridine derivatives are highly reactive in the presence of basic reaction partners,[4] and this functionality in our case had to survive the conditions of epimerization. The advantage of the discussed route is that no protecting and consequently no deprotecting steps are involved.

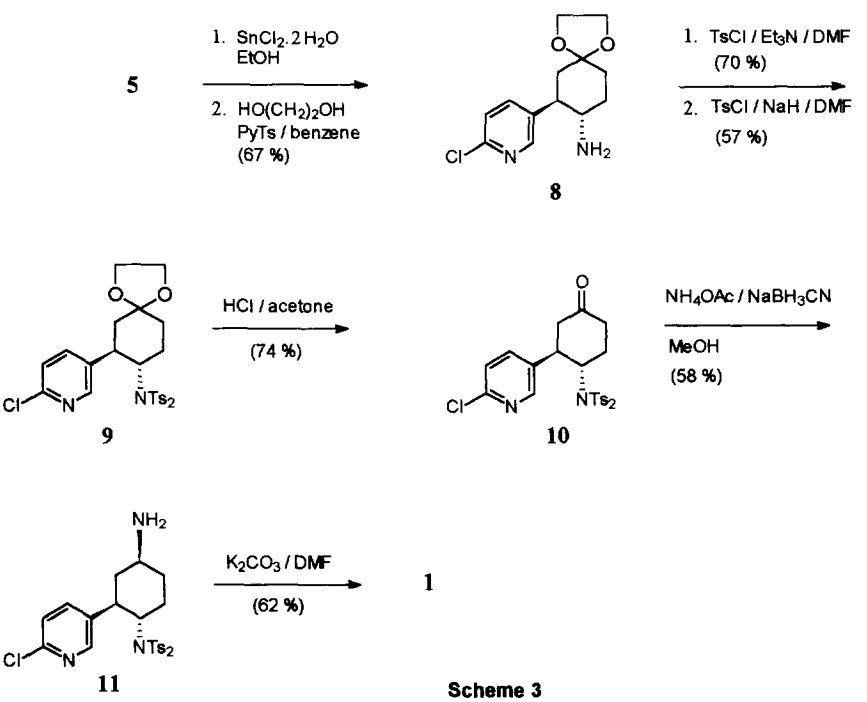
We had two reasons to modify the above described reaction sequence: a) the combined yield in the last two steps is only 30%; b) we encountered derivatives having other substituents in the place of the

chloropyridine ring which were reluctant to epimerize under the given conditions. The easiest modification of the reaction sequence depicted in Scheme 1 adopted was based on a reverse reactivity ("*Umpolung*") approach. Thus ring closure as shown in Scheme 2, transposition of the amino and leaving group on the cyclohexane ring would give the opposite configuration.



Scheme 2

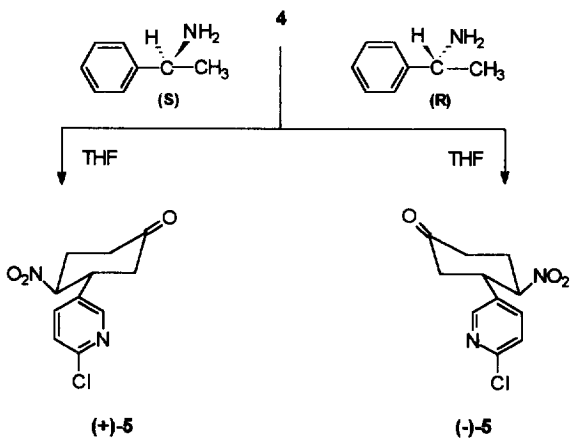
Thus nitro group in compound **5** was reduced first (Scheme 3). Subsequent treatment with ethylene glycol furnished the protected amino ketone **8**. The "*Umpolung*" of the reactivity of the amino group was reached by ditosylation. The protected keto group of compound **9** so obtained was deprotected yielding **10**. The oxo-function was changed to amine by applying reductive amination (**11**), then base-catalyzed ring closure was performed supplying racemic epibatidine (**1**).



Scheme 3

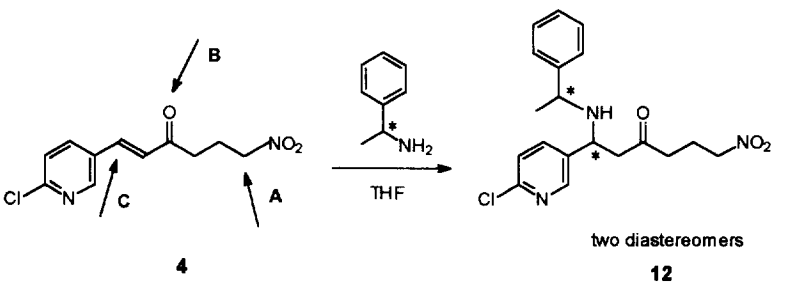
To prepare optically active epibatidine several routes were investigated. The *endo*-isomer **1'** was resolved with di-toluyl-tartaric acid, the same acid as used also by Huang and Shen[3b] for resolving **1**. The nitro-alcohol obtained by reduction of ketone **5** was transformed into (-)-menthyl esters (**6c**, **6d**). Subsequent separation and hydrolysis of **6c** gave the optically active nitroalcohol (+)-**6a**. (The other diastereomeric form **6d** could not be entirely purified from its **6c** component).

Clearly an *enantioselective* synthesis would be the most useful and most elegant solution to the problem. The prochiral nitro-ketone **4** was treated with different optically active amines instead of potassium fluoride. It turned out that only primary amines yielded the optically active cyclized product **5**, and the best optical yield (>80%) was achieved by using optically active α-phenyl ethyl amines. The absolute configuration corresponding to the natural product was obtained by applying the amine with **R** configuration (Scheme 4).



Scheme 4

As far as the mechanism of the amine-catalyzed ring closure is concerned, we considered three plausible possibilities (Scheme 5).



Scheme 5

According to mechanism *A*, formation of a salt with the acidic proton α to the nitro group would occur followed by ring closure of the salt. Since only primary amines were effective, there is a possibility of the formation of a Schiff-base as an intermediate (mechanism *B*) may be significant. However, our experimental results showed that at the outset two diastereoisomers (**12**) are formed through addition of the amine to the

C=C double bond (mechanism *C*). The adducts, although not in their entirely pure form, could be isolated. On dissolving and warming **12** in $CDCl_3$, the adducts lose the amine and the starting components **4** and α-phenyl ethyl amine are recovered, while at room temperature the expected ring closure yields **5**. Clearly, however, the possibility that adduct **12** is a side product rather than an intermediate still exists, and further investigations into the extension of the enantioselective reaction to other models and studies of the mechanism are in progress.

Experimental Section

Melting points are uncorrected. Optical rotations were recorded in chloroform at 25±2 °C. IR spectra were taken on a Nicolet 7795 FT-IR spectrometer. Mass spectra were run on an AEI-MS-902 (70 eV; direct insertion) mass spectrometer. NMR measurements were carried out on a Varian UNITYplus 500 instrument (500 MHz for ^1H) at 30 °C or on a Varian VXR-300 instrument (300 MHz for ^1H) at 24 °C.

Starting materials. Commercially available compounds from Aldrich, Kieselgel 60 (0.063-0.200 mm) silica gel for column chromatography and TLC plates (No. 5554) from Merck were purchased.

(5-Nitropentane-2-one)-triphenyl-phosphonium bromide **(3)**. To a stirred solution of 1-nitropentane-4-one (**2**) (80.0 g, 0.61 mole) in methanol (250 ml) bromine (31.5 ml, 0.61 mole) was added dropwise during ice cooling while the reaction temperature was kept at 25-30 °C. After 2 h water (250 ml) was added and the stirring was continued overnight. The reaction mixture was then extracted with ether (3 x 300 ml), the combined organic extracts washed with 10 % $NaHCO_3$ (3 x 200 ml) and water (3 x 200 ml), dried ($CaCl_2$), filtered and evaporated. The residue was chromatographed (eluent: hexane + EtOAc, 3/1; TLC R_f = 0.3) to give 1-bromo-nitropentane-2-one (70.4 g, 55%) as a pale yellow oil. The obtained bromine compound was dissolved in dry benzene (200 ml) to which a solution of triphenyl phosphine (96.77 g, 0.369 mole) in dry benzene (350 ml) was added dropwise. The reaction mixture was stirred at room temperature for 48 h whereby the oily precipitate became crystalline. The salt was filtered and washed (hexane) to yield compound **3** (140.8 g, 89%), mp: 70-72 °C.

1-[3-(6-Chloropyridyl)]-3-oxo-6-nitrohexa-1-ene **(4)**. A solution of salt **3** (22.8 g, 48.1 mM) in CH_2Cl_2 (450 ml) was treated with 1% NaOH (450 ml) to yield (5-nitropentane-2-one)-triphenyl-phosphorane (13.5 g, 34.4 mM), mp: 94-97 °C. IR (KBr): 1540, 1440, 1400, 1110 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): 2.33 quint. (2H); 2.44 t (2H); 4.51 t (2H); 7.43-7.70 m (16H).

To a solution of this phosphorane in CH_2Cl_2 (70 ml) a solution of 6-chloropyridine-3-carboxaldehyde (3.1 g, 22.0 mM) in CH_2Cl_2 (70 ml) was added. The reaction mixture was refluxed for 8 h under Ar. After cooling the solvent was evaporated and the residue chromatographed (eluent: hexane + EtOAc, 1/1) to give compound **4** (4.7 g, 84%), mp: 97-100 °C. IR (KBr): 1700, 1680, 1620, 1580, 1550, 1100 cm^{-1}. MS (*m/z*; %): 254 (M^+, 3.5); 166 (100); 138 (24.7); 102 (22.1); 77 (9.7). ^1H NMR (300 MHz, $CDCl_3$): 2.38 quint. (2H); 2.86 t (2H); 4.51 t (2H); 6.77 d (1H); 7.39 d (1H); 7.53 d (1H); 7.84 dd (1H); 8.54 d (1H).

(±)-1α-Nitro-2β-[3-(6-chloropyridyl)]-cyclohexane-4-one **(5)**. Compound **4** (1.9 g, 7.46 mM) was dissolved in dry THF (50 ml) and KF/Al_2O_3 (3.5 g, 14.9 mM) was added. The reaction mixture was stirred at

rt overnight then the solid product was filtered and the filtrate evaporated. The residue was purified by chromatography (eluent: hexane + EtOAc, 1/1), to give compound **5** (1.1 g, 59%), mp: 118-121 °C. IR (KBr): 1710, 1680, 1585, 1550, 1100 cm^{-1}. MS (*m/z*; %): 254 (M^+, 2.6); 165 (40.3); 77 (13.2); 55 (17.7). ^1H NMR (500 MHz, $CDCl_3$): 2.44-2.75 m (6H); 3.73 ddd (1H); 5.02 td (1H); 7.34 d (1H); 7.54 dd (1H); 8.31 d (1H).

(±)-1α-Nitro-2β-[3-(6-chloropyridyl)]-cyclohexane-4-β-ol **(6a)**. To a suspension of compound **5** (2.8 g, 11.0 mM) in EtOH (200 ml) $NaBH_4$ (1.2 g, 31.7 mM) was added in small portions (1.5 h). The excess reducing agent was quenched by careful addition of acetone, the reaction mixture was evaporated and the residue was chromatographed (eluent: $CHCl_3$ + MeOH, 10/1) to yield compound **6a** (1.9 g, 67%), mp: 149-153 °C. IR (neat) = 3380, 1580, 1570, 1550, 1100, 1080 cm^{-1}. MS (*m/z*; %): 256 (M^+, 3.5); 209 (33.6); 191 (100); 126 (65.4); 77 (13.2). ^1H NMR (300 MHz, $CDCl_3$): 1.48-1.71 m (2H); 1.94 br s (1H); 2.10 m (1H); 2.18-2.30 m (2H); 2.46 dq (1H); 3.30 ddd (1H); 4.59 td (1H); 7.30 d (1H); 7.51 dd (1H); 8.25 d (1H).

(±)-1α-Nitro-2β-[3-(6-chloropyridyl)]-4-β-methanesulfonyloxy-cyclohexane **(6b)**. Compound **6a** (1.0 g, 3.4 mM) was dissolved in a mixture of dry CH_2Cl_2 (15 ml) and dry pyridine (70 ml), then methanesulfonyl chloride (0.75 ml, 9.7 mM) was added dropwise at 0 °C. The reaction mixture was stirred overnight at rt then evaporated. The residue was purified by chromatography (eluent: hexane + EtOAc, 1/1) to give compound **6b** (1.2 g, 91%), mp: 120-122 °C. IR (KBr): 1590, 1570, 1540, 1530, 1450, 1350, 1180, 1090 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): 1.82 m (1H); 1.90 m (1H); 2.15 m (1H); 2.45 m (1H); 2.53 dq (1H); 3.04 s (3H); 3.37 m (1H); 4.62 td (1H); 4.83 m (1H); 7.30 d (1H); 7.50 dd (1H); 8.27 d (1H).

(-)-1α-Nitro-2β-[3-(6-chloropyridyl)]-cyclohexane-4-β-ol-carbonic acid menthyl ester (1S,2S,4R,1'R,2'S,5'R) **(6c)**. Compound **6a** (1.536g, 6.0 mM) was dissolved in a mixture of dry CH_2Cl_2 (30 ml) and dry pyridine (1.4 ml), then (-)-menthyl chloroformate (3.0 ml, 14.0 mM) was added dropwise at 0 °C. The reaction mixture was stirred for 6 h at rt then a further portion of reagent (0.2 ml) was added. The mixture was stirred overnight then evaporated. The residue was dissolved in $CHCl_3$ (60 ml) and water (10 ml), then the pH was adjusted to 9 (5% $NaHCO_3$ solution). The two phases were separated, the organic phase was washed with water (3 x 20 ml), dried (Na_2SO_4) and evaporated. The residue was crystallized from methanol (100 ml) to give a crude product (1.2 g; 49%), mp: 98-100 °C, $[\alpha]_D^{25}$ = (-)-56.0 ° (c = 0.5, $CHCl_3$). The precipitated product was purified by column chromatography (eluent: benzene + EtOAc, 19/1). The solvent was evaporated under reduced pressure and the residue (oil, 0.63 g) was crystallized from methanol (10 ml) to give **6c** (0.28 g), mp: 183-184 °C, $[\alpha]_D^{25}$ = (-)-36.7 ° (c = 0.5, $CHCl_3$). IR (KBr): 1710, 1540 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 0.75 d (3H); 0.88 d (3H); 0.93 d (3H); ~0.86 m (1H); 1.05 m (1H); 1.06 m (1H); 1.39 m (1H); 1.48 m (1H); 1.63-1.81 m (4H); 1.88 m (1H); 2.06 m (1H); 2.15 m (1H); 2.32-2.42 m (2H); 2.51 dq (1H); 3.37 m (1H); 4.52 td (1H); 4.62 td (1H); 4.78 m (1H); 7.30 d (1H); 7.51 dd (1H); 8.28 d (1H).

After the first crystallization the mother liquor was evaporated to dryness and the residue was purified by column chromatography (eluent: benzene + EtOAc, 19/1). The solvent was evaporated under reduced pressure and the residue (oil, 1.2 g, 49%) was crystallized from diisopropyl ether (20 ml) to give the diastereomeric mixture **6d** + **6c** (crude product, 0.71 g), mp: 165-193 °C, $[\alpha]_D^{25}$ = (-)-42.1 ° (c = 0.5, $CHCl_3$). The precipitated crystals were recrystallized (isopropanol, five times) until the optical rotation did not change further to give **6d**+**6c** as a 3:1 mixture of two diastereoisomers (0.27 g), mp: 165-185 °C, $[\alpha]_D^{25}$ = (-)-46.0 ° (c = 0.5, $CHCl_3$). IR (KBr): 1710, 1540 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): the ^1H spectra of **6d** and **6c** are

essentially identical (see the data given for **6c** above) except for the Me chemical shifts which for **6d** are as follows: 0.80 d (3H); 0.91 d (3H).

(±)-1α-Amino-2β-[3-(6-chloropyridyl)]-4-β-methanesulfonyloxy-cyclohexane (**7**). To a solution of compound **6b** (1.5 g, 4.8 mM) in EtOH (150 ml) $SnCl_2.2H_2O$ (13.0 g, 57.6 mM) was added. The reaction mixture was refluxed for 24 h. After cooling the pH was adjusted to 9 (cc. NH_4OH), the precipitate was filtered and washed ($CHCl_3$). The filtrate was washed with water (2 x 200 ml) and brine (200 ml), dried ($MgSO_4$) then evaporated to give compound **7** (1.1 g, 80%) as a slightly yellow oil which was applied in the next step without further purification.

(±)-endo-Epibatidine (**1'**). A solution of compound **7** (1.1 g, 3.6 mM) in dry toluene (150 ml) was refluxed under Ar overnight. After cooling a 10 % NaOH solution (25 ml) was added, the phases were shaken then separated. The aqueous phase was extracted with CH_2Cl_2 (5 x 25 ml), the combined organic phase was washed with brine (100 ml), dried ($MgSO_4$) and evaporated. The residue was chromatographed (eluent: $CHCl_3$ + MeOH + NH_4OH, 10/1/0.1) to give (±)-**1'** (350 mg, 46%) as a faint yellow oil. IR (neat): 3260, 3220, 1580, 1560, 1200, 1100 cm^{-1}. MS (*m/z*; %): 208 (M^+, 8.8); 140 (12.3); 69 (100).

(±)-exo-Epibatidine (**1**). To a solution of compound **1'** (200 mg, 0.95 mM) in *t*-BuOH (30 ml) $KOBu^t$ (1.0 g, 8.91 mM) was added and the reaction mixture was refluxed under Ar for 30 h. After cooling the mixture was evaporated, the residue was chromatographed (eluent: $CHCl_3$ + MeOH + NH_4OH, 10/1/0.1) to yield (±)-**1** (100 mg, 50%) as a colorless oil.

(±)-1α-Amino-2β-[3-(6-chloropyridyl)]-cyclohexane-4-one-ethylene ketale (**8**). To a solution of compound **5** (2.54 g, 10.0 mM) in EtOH (250 ml) $SnCl_2.2H_2O$ (27.0 g, 120 mM) was added and the reaction mixture was refluxed for 24 h. After cooling the mixture was evaporated, ethylene glycol (50 ml), benzene (250 ml) and pyridinium tosylate (2.5 g) were added to the residue. The reaction mixture was refluxed for about 6 h until no more water escaped. After cooling the two phases were separated, the ethylene glycol phase was made alkaline by cc. NH_4OH, the precipitate was filtered and washed ($CHCl_3$). The filtrate was washed with water (2 x 200 ml) and brine (200 ml), dried ($MgSO_4$) then evaporated. The residue was purified by chromatography (eluent: $CHCl_3$ + MeOH, 10/1) to give compound **8** (1.79 g, 67 %), colorless oil. IR (neat): 3180, 2980, 2840, 1580, 1540, 1460, 1400, 1100 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 1.50-2.08 m (6H); 2.80 td (1H); 2.97 ddd (1H); 3.90-4.00 m (4H); 7.31 d (1H); 7.56 dd (1H); 8.29 d (1H).

(±)-1α-Ditosylamino-2β-[3-(6-chloropyridyl)]-cyclohexane-4-one-ethylene ketale (**9**). To a solution of compound **8** (4.0 g, 14.9 mM) in dry DMF triethylamine (4.2 ml, 30.12 mM) and *p*-toluenesulfonyl chloride (5.68 g, 29.76 mM) were added. The reaction mixture was stirred at rt for 1 h, then poured into ice-cold water (500 ml), the precipitated product was filtered, dried and recrystallized (EtOH). The pure monotosylated product (4.4 g, 70%, mp: 182-184 °C) was dissolved in dry DMF (250 ml), and NaH (1.5 g, 31.2 mM) was added in small portions. The reaction mixture was stirred at rt for 0.5 h, then *p*-toluenesulfonyl chloride (5.95 g, 31.2 mM) was added. Stirring was continued for 2 h, then the reaction mixture was poured into ice-cold water (2000 ml). The precipitated product was filtered, dried and purified by column chromatography (eluent: hexane + EtOAc, 1/1) to yield compound **9** (4.6 g, 57 %) mp: 210-213 °C. IR (KBr): 3020, 2980, 2960, 2930,

1470, 1380, 1220, 1170, 1090, 750 cm^{-1}. MS (*m/z*; %): 422 (M^+–154, 7); 379 (2.6); 282 (5.3); 212 (100); 128 (87.6); 91 (30). ^1H NMR (300 MHz, $CDCl_3$): 1.80-2.08 m (5H); 2.44 s (3H); 2.61 ddd (1H); 3.25 s (3H); 3.83 ddd (1H); 3.90-4.01 m (4H); 4.52 ddd (1H); 7.35 d (1H); 7.69 dd (1H); 8.43 d (1H).

(±)-1α-Ditosylamino-2β-[3-(6-chloropyridyl)]-cyclohexane-4-one **(10)**. To a solution of compound **9** (4.0 g, 6.93 mM) in acetone (200 ml) cc. HCl (10 ml) was added. The reaction mixture was heated to boiling while the acetone was continuously distilled off and the distillate was replaced by adding fresh acetone dropwise. After 4 h the reaction mixture was cooled, dissolved in $CHCl_3$ (200 ml), then the pH was adjusted to 9 (10 % NaOH). The two phases were separated, the aqueous phase was extracted with $CHCl_3$ (2 x 100 ml), the combined organic phase was washed with water (2 x 200 ml) and saturated brine (200 ml), dried ($MgSO_4$) and evaporated. The residue was chromatographed (eluent: benzene + MeOH, 10/1) to give compound **10** (2.66 g, 74 %) as a colorless oil. IR (neat): 3020, 3000, 1710, 1580, 1560, 1550, 1380, 1360, 1340, 1350, 1180, 1150, 800 cm^{-1}. MS (*m/z*; %): 532 (M^+, 7); 377 (31.8); 294 (4.4); 238 (23); 207 (23); 155 (82.3); 91 (100). ^1H NMR (300 MHz, $CDCl_3$): 2.36 m (1H); 2.56 s (3H); 2.60-2.75 m (5H); 3.24 s (3H); 3.94 ddd (1H); 4.97 ddd (1H); 7.41 d (1H); 7.72 dd (1H); 8.46 d (1H).

(±)-4β-Amino-1α-ditosylamino-2β-[3-(6-chloropyridyl)]-cyclohexane **(11)**. To a suspension of compound **10** (2.0 g, 3.75 mM) MeOH (300 ml) NH_4OAc (2.89 g, 37.51 mM) and $NaBH_3CN$ (0.24 g, 3.75 mM) were added. The reaction mixture was stirred at rt for 2 h then quenched by adding a few drops of acetone. After evaporation the residue was dissolved in $CHCl_3$ (200 ml) and water (100 ml). The two phases were separated, the organic phase was washed with water (2 x 100 ml) and saturated brine (100 ml), dried ($MgSO_4$) and evaporated. The residue was chromatographed (eluent: $CHCl_3$ + MeOH, 5/1) to give compound **11** (1.16 g, 58 %), mp: 158-162 °C. IR (KBr): 3280, 3220, 3300, 1450, 1380, 1320, 1150, 760 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, characteristic signals): 2.42 s (3H); 2.50 s (3H); 3.03 m (1H); 3.79 td (1H); 4.05 td (1H); 6.92 d (1H); 7.20 dm (2H); 7.26 dm (2H); 7.43 dd (1H); 7.55 dm (2H); 7.77 dm (2H); 8.06 d (1H).

(±)-exo-Epibatidine **(1)**. To a solution of compound **11** (1.0 g, 1.87 mM) in dry DMF (50 ml) dry K_2CO_3 (0.78 g, 5.61 mM) was added. The reaction mixture was refluxed under Ar for 1 h. After cooling the mixture was evaporated, the residue chromatographed (eluent: $CHCl_3$ + MeOH + NH_4OH, 10/1/0.1) to yield (±)-**1** (0.24 g, 62%).

1R,1'R-1-[3-(6-Chloropyridyl)]-2-[-1'-(1'-phenyl-ethylamino)]-3-oxo-6-nitro-hexane and 1S,1'R-1-[3-(6-chloropyridyl)]-2-[-1'-(1'-phenyl-ethylamino)]-3-oxo-6-nitro-hexane **(12)**. To a solution of compound **4** (8.0 g, 31.41 mM) in dry THF (80 ml) (+)-α-phenyl ethylamine (20.2 ml, 156.7 mM) was added. The reaction mixture was kept in refrigerator for 3 days then evaporated. The residue was twice chromatographed (eluents: benzene + MeOH, 10/1 and hexane + EtOAc, 1/1, respectively), to give a ca. 3/2 molar mixture of **12** diastereoisomers together with **4** (3.8 g, 32 %) as a very unstable oil which decomposes easily to the starting materials. ^1H NMR (300 MHz, $CDCl_3$, characteristic signals): 1.26 d (3H); [1.35 d (3H)]; 3.36 q (1H); [3.59 q (1H)]; 3.83 dd (1H); [4.25 dd (1H)], [signals due to the minor diastereoisomer are denoted by brackets, those due to **4** are not listed].

(-)-(1R,2R)-1-Nitro-2-[3-(6-chloropyridyl)]-cyclohexane-4-one **(-/-/-5)**. To a solution of compound **4** (8.0 g, 31.41 mM) in dry THF (80 ml) (+)-α-phenyl ethylamine (20.2 ml, 156.7 mM) was added. The reaction

mixture was kept at rt for 3 days then evaporated. The residue was twice chromatographed (eluents: benzene + MeOH, 10/1, and hexane + EtOAc, 1/1) to give compound (-)-**5** (4.3 g, 54 %), $[\alpha]_D^{25}$ = (-)-69.6 ^{o} (c=1.0, $CHCl_3$), ee = 80 %. A single recrystallization from EtOH provided the optically pure product (-)-**5** (3.3 g, 41%), $[\alpha]_D^{25}$ = (-)-87.2 ^{o} (c = 1.0, $CHCl_3$), mp: 147-149 ^{o}C. The optical purity was verified by recrystallization and ^{1}H NMR (500 MHz, $CDCl_3$) shift reagent measurements as follows. Racemic **5** (5 mg) was dissolved in $CDCl_3$. Optically active shift reagent (SR) tris[3-(trifluoromethyl-hydroxymethylene)-(+)-camphorato], europium (III) was gradually added to the sloution. Although the induced shifts were in general relatively small, a 17 Hz separation of the (+) and (-) forms were observed on the H-3 signal of the 2-chloropyridine ring on adding 80 mg of SR. The further addition of SR gave no significant increase in the line separation, but the line-broadening effect became inconvenient for the purposes of enantiomeric excess determination. [Other signals proved to be unsuitable for ee measurement throughout the whole range of added SR due to insufficient induced shift, signal overlap or extensive line broadening. Measurements undertaken at a lower field (300 MHz) yielded essentially the same results]. From the ^{1}H NMR spectrum of a mixture of 5 mg of substrate and 80 mg of SR, the active form of **5** was determined to have at least 90 % optical purity.

(+)-(1S,2S)-1-Nitro-2-[3-(6-chloropyridyl)]-cyclohexane-4-one (**/+/-5**). To a solution of compound **4** (8.0 g, 31.41 mM) in dry THF (80 ml) (-)-α-phenyl ethylamine (20.2 ml, 156.7 mM) was added. The reaction mixture was allowed to stand at rt for 3 days then evaporated. The residue was chromatographed (eluents: benzene + MeOH, 10/1 and hexane + EtOAc, 1/1) to give compound (+)-**5** (4.2 g, 53%), $[\alpha]_D^{25}$ = (+)-60.3 ^{o} (c = 1.0, $CHCl_3$), ee = 69 %. A single crystallization from EtOH provided the optically pure product (+)-**5** (2.9 g, 36%), $[\alpha]_D^{25}$ = (+)-83.4 ^{o} (c = 1.0, $CHCl_3$), mp: 148-149 ^{o}C. The optical purity was verified by recrystallization.

The following optically pure intermediates were synthesized according to Scheme 1.

(-)-1R,2R,4S-1-Nitro-2-[3-(6-chloropyridyl)]-cyclohexane-4-ol (**/-/-6a**). Yield 62%, $[\alpha]_D^{25}$ = (-)-77.4 ^{o} (c = 0.5, $CHCl_3$), mp: 192-194 ^{o}C.

(+)-1S,2S,4R-1-Nitro-2-[3-(6-chloropyridyl)]-cyclohexane-4-ol (**/+/-6a**). To a solution of compound **6c** (100 mg; 0.227 mM) in ethanol (20 ml) sulfuric acid solution (20%, 20 ml) was added. The reaction mixture was refluxed for 24 h, then concentrated under reduced pressure. To the residue benzene (30 ml) was added and evaporated again 5-6 times. The dry residue was dissolved in $CHCl_3$ (20 ml) and water (5 ml), then the pH was adjusted to 10 (cc. NH_4OH solution). The two phases were separated, the organic phase was washed with water (5 ml), dried (Na_2SO_4) and evaporated. The residue was chromatographed (eluent: $CHCl_3$ + MeOH, 19/1) to yield (+)-**6a** (32 mg; 55%), mp: 190-194 ^{o}C, $[\alpha]_D^{25}$ = (+)-74.9 ^{o} (c = 1.0, $CHCl_3$).

(-)-1R,2R,4S-1-Nitro-2-[3-(6-chloropyridyl)]-4-methanesulfonyloxy-cyclohexane (**/-/-6b**). Yield 71%, $[\alpha]_D^{25}$ =(-)-21.9 ^{o} (c = 1.0, $CHCl_3$), colorless oil.

(+)-1R,2S,4S-Epibatidine (**/+/-1'**). Yield 32%, $[\alpha]_D^{25}$ = (+)-44.8 ^{o} (c = 0.5, MeOH), colorless oil.
(-)-1R,2R,4S-Epibatidine (**/-/-1**). Yield 50%, $[\alpha]_D^{25}$ = (-)-8.5 ^{o} (c = 1.2, $CHCl_3$); for lit. $[\alpha]_D$ values see: ref. 3b, 3d, 3f, 3p; mp: 52-53 ^{o}C.

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