ISSN 1070-4280, Russian Journal of Organic Chemistry, 2009, Vol. 45, No. 7, pp. 1050–1060. © Pleiades Publishing, Ltd., 2009.
Original Russian Text © I.S. Veselov, I.V. Trushkov, N.S. Zefirov, G.V. Grishina, 2009, published in Zhurnal Organicheskoi Khimii, 2009, Vol. 45, No. 7, pp. 1062–1072.

trans-4-Amino-3-hydroxypiperidines. Regio- and Stereoselective Synthesis

I. S. Veselov, I. V. Trushkov, N. S. Zefirov, and G. V. Grishina

Faculty of Chemistry, Moscow State University, Vorob'evy gory 1, Moscow, 119992 Russia
e-mail: grishina@org.chem.msu.ru

Received February 5, 2008

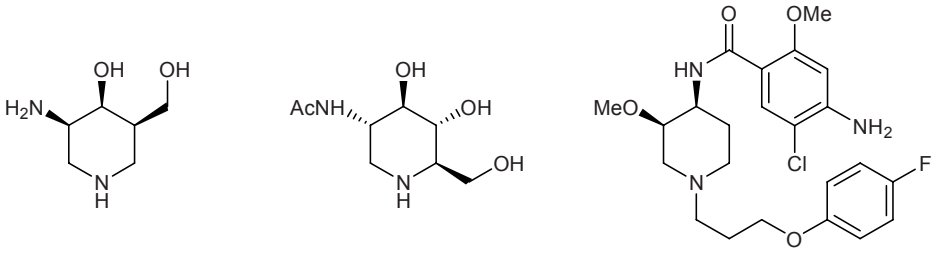
Abstract—*trans*-4-Amino-1-benzyl-3-hydroxypiperidines were synthesized by regio- and stereoselective amination of a series of 1-benzyl-3,4-epoxypiperidines with primary and secondary aliphatic, aromatic, and heterocyclic amines in the presence of lithium perchlorate. The regio- and stereoselectivity of the amination process is ensured by specific activation of the oxirane ring in epoxypiperidine derivatives. Lithium cation is coordinated simultaneously at the piperidine nitrogen atom and oxirane oxygen atom, which leads to greater extension of the C^4–O bond as compared to C^3–O, so that nucleophilic attack is directed at the C^4 atom of the piperidine ring.

DOI: 10.1134/S1070428009070124

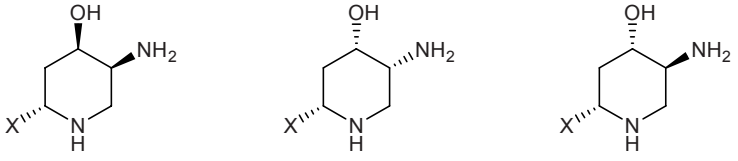
Numerous amino-and-hydroxy-substituted piperidine derivatives constitute a subclass of hydroxylated piperidine alkaloids or imino (aza) sugars and are known as potent inhibitors of a number of glucosidases and related enzymes. The presence of an amino group in their molecules ensures selective inhibition of particular glucosidases and hexosaminidases. For example, 2-deoxy-2-aminoisofagomine (**I**) selectively inhibits β-glucosidase [1], while 1-deoxynojirimycin analog **II** selectively inhibits β-*N*-acetylglucosaminidase [2]. Cisapride (**III**) is a serotonin (5-HT) receptor blocker which is used to stimulate intestinal peristalsis without side antagonistic effect on the D_2 dopamine receptors [3, 4].

In the recent time, much attention was also given to alkaloids pseudodistomins **A**–**F** which were isolated from marine organisms and were shown to exhibit anticancer activity [5–8].

Taking into account the above stated, β-amino-substituted hydroxy piperidines are promising not only

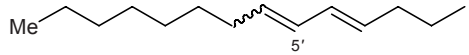
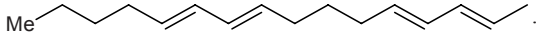


I **II** **III**



A, **B**, **F** **C**, **E** **D**

A, X = R^1, 5′-*cis*; **B**, **D**, **E**, X = R^1, 5′-*trans*; **C**, **F**, X = R^2;

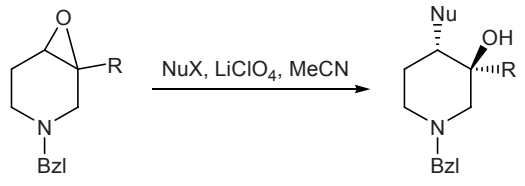
R^1 =  ; R^2 =  .

from the viewpoint of design of synthetic amino sugar analogs but also as multipurpose building blocks in fine organic synthesis. Despite so wide potential of 3- and 4-amino hydroxy piperidines, only a few methods of synthesis of such compounds have been reported up to now [9, 10]; these methods are based on transformations of natural sugars so that they ensure preparation of only one stereoisomer via very tedious and multistep synthetic procedures [11–13].

In the present article we describe a short regio- and stereoselective synthesis of *trans*-4-amino-3-hydroxypiperidines by aminolysis of 1-benzyl-3,4-epoxypiperidines; an efficient procedure for the preparation of the latter was developed by us previously [14]. Nucleophilic opening of the oxirane ring in 1-acyl- or 1-carbamoyl-3,4-epoxypiperidines in various media under different conditions is not selective, and the products are mixtures of the corresponding 3- and 4-substituted isomers [15–18]. There are almost no published data on the aminolysis of *N*-alkyl-3,4-epoxypiperidines.

The reactions of epoxy derivatives **IV** and **V** with an equimolar amount of aliphatic, aromatic, or heterocyclic amine in acetonitrile in the presence of 1 equiv of lithium perchlorate at room temperature gave only the corresponding *trans*-4-amino-3-hydroxypiperidines **VI**–**XIX** (Scheme 1). No oxirane ring opening occurred in the absence of Lewis acid. The progress of the reactions was monitored by TLC following disappearance of the initial epoxide. The reaction time strongly depended on the nucleophile structure and its basicity (Table 1). In all cases, analysis of the reaction mixtures by gas chromatography–mass spectrometry revealed formation of only one compound with *m*/*z* value of the molecular ion corresponding to the target amino alcohol. Individual amino alcohols **VI**–**XIX** were isolated as free bases or hydrochlorides, and their purity was confirmed by elemental analysis.

Scheme 1.



IV, **V** **VI–XXII**

IV, **VI**–**XVI**, **XX**–**XXII**, R = H; **V**, **XVII**–**XIX**, R = Me; **VI**, **XVII**, Nu = $PhCH_2NH$; **VII**, Nu = EtNH; **VIII**, Nu = *cyclo*-$C_6H_{11}CH_2NH$; **IX**, Nu = morpholino; **X**, Nu = 4-methylpiperazin-1-yl; **XI**, Nu = 4-(pyridin-2-yl)piperazin-1-yl; **XII**, Nu = azepan-1-yl; **XIII**, Nu = 4-hydroxypiperidino; **XIV**, Nu = Et_2N; **XV**, **XIX**, Nu = PhNH; **XVI**, Nu = 2-FC_6H_4NH; **XVIII**, Nu = pyrrolidin-1-yl; **XX**, Nu = CN; **XXI**, Nu = N_3, **XXII**, Nu = PhS.

Table 1. Conditions of synthesis, yields, and some ^{1}H NMR parameters of amino alcohols **VI**–**XXII**

Comp. no.	Reaction time, days	Yield, %	$^3J_{3\text{-}ax,4\text{-}ax}$, Hz	δ(3-H_{ax}), ppm	δ(4-H_{ax}), ppm
VI	1	86	9.1	3.43	2.33
VII	1	82	8.9	3.31	2.20
VIII	1	93	9.1	3.37	2.21
IX	2	88	9.8	3.59	2.18
X	2	83	10.0	3.58	2.20
XI	2	95	9.9	3.66	2.29
XII	2	89	9.9	3.49	2.21
XIII[a]	2	81	9.6	3.57	2.17
XIV	3	52	9.8	3.51	2.28
XV	1	83	8.2	3.54	3.19
XVI	3	67	7.9	3.64	3.25
XVII	3	88	–	–	2.43
XVIII	7	76	–	–	2.34
XIX	4	75	–	–	3.36
XX	7	51	7.0	3.92	2.60
XXI	7	56	7.9	3.60	3.31
XXII	0.3	69	7.7	3.58	2.93

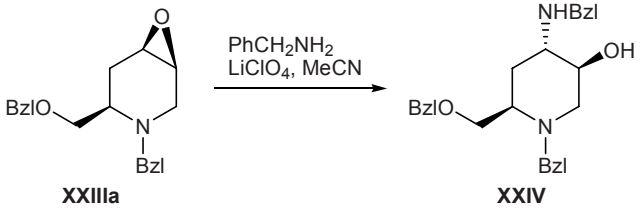
[a] Data of [19].

The ^{13}C NMR spectrum of amino alcohol **VI** was consistent with the assumed structure. The signal at δ_C 70.7 ppm was assigned to the carbon atom linked to the hydroxy group, i.e., the aminolysis of **IV** with benzylamine actually involves opening of the oxirane ring. However, it remained to elucidate which of the possible regio- and stereoisomers was obtained.

Using double resonance techniques we assigned all signals observed in the ^{1}H NMR spectrum of amino alcohol **VI**. The triplet at δ 1.96 ppm ($^3J_{2\text{-ax},\ 3\text{-ax}} \approx$ 10 Hz) was assigned to the axial proton on C^2; irradiation at a frequency corresponding to resonance of 2-H_{ax} gave responses on the 2-H_{eq} (δ 2.98 ppm) and 3-H_{ax} signals (δ 3.43 ppm). The most downfield signal from protons in the piperidine ring (δ 3.43 ppm) arises from the axial proton on the C^3 atom linked to the hydroxy group. These data indicate that amino alcohol **VI** is 4-amino-3-hydroxy isomer. The coupling constant $^3J_{3\text{-}ax,4\text{-}ax}$ = 9.1 Hz suggests axial orientation of protons on C^3 (δ 3.43 ppm) and C^4 (δ 2.33 ppm) and hence equatorial orientation of the 3-hydroxy and 4-amino groups. Thus amino alcohol **VI** has the structure of *trans*-4-benzylamino-3-hydroxypiperidine, i.e.,

cleavage of the oxirane ring in 3,4-epoxypiperidine **IV** with benzylamine in the presence of lithium perchlorate is completely regio- and stereoselective. We also found that the 3-H signal in the ^{1}H NMR spectra of all amino alcohols **VI**–**XXII** is located in the region δ 3.4–3.6 ppm, which is typical of a CH group linked to OH. The signal from 4-H in alkylamino derivatives **VI**–**VIII** appears at δ 2.2–2.3 ppm, and the corresponding signal from arylamino derivatives **XVI** and **XIX** is observed at δ 3.2–3.3 ppm. Therefore, aminolysis of 3,4-epoxypiperidines with all the examined amines is characterized by complete regio- and stereoselectivity (Table 1).

Scheme 2.



XXIIIa **XXIV**

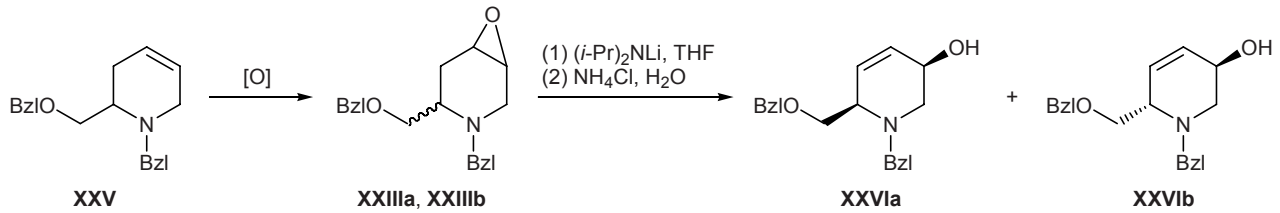
The reactions of epoxypiperidine **IV** with other nucleophiles (benzenethiol, sodium azide, and sodium cyanide) were also completely regio- and stereoselective, and they led to the formation of only *trans* isomers **XX**–**XXII** (Scheme 1, Table 1). Likewise, the aminolysis of *cis*-6-benzyloxymethyl-3,4-epoxypiperidine (**XXIIIa**) gave *trans*-amino alcohol **XXIV** as the only product (Scheme 2). Initial epoxypiperidine **XXIIIa** was synthesized by treatment of diastereoisomer mixture **XXIIIa**/**XXIIIb** [14] with 1.1 equiv of lithium diisopropylamide (LDA). In this case, the rearrangement involved only the more reactive isomer **XXIIIb**, whereas less reactive *cis* isomer **XXIIIa** remained unchanged, and it can readily be isolated from the reaction mixture by column chromatography on silica gel (yield 45%; Scheme 3; Table 2, run no. 3). In the presence of double amount of LDA both isomeric epoxides **XXIIIa** and **XXIIIb** were transformed into allyl-type alcohols **XXVIa** and **XXVIb** with different conversions. According to the ^{1}H NMR data, the reaction mixture contained approximately equal amounts of epoxide **XXIIIa** and isomeric alcohols **XXVIa** and **XXVIb** (Table 2, run no. 1).

Thus we have developed a simple procedure for regio- and stereoselective opening of the oxirane ring in 1-benzyl-3,4-epoxypiperidines with nitrogen-, carbon-, and sulfur-centered nucleophiles. Our results radically differ from published data on reactions of *N*-acyl- and *N*-carbamoyl-3,4-epoxypiperidines with nucleophiles, which are always nonselective (mixtures of the corresponding 3- and 4-substituted isomers are formed).

We then tried to elucidate factors ensuring high regio- and stereoselectivity in the reactions of epoxypiperidines with N-, C- and S-nucleophiles in the presence of lithium perchlorate using as model substrates compound **IV** and isomeric 1-benzyl-6-benzyloxymethyl- and 1-benzyl-6-methyl-3,4-epoxypiperidines **XXIIIa**/**XXIIIb** and **XXVIIa**/**XXVIIb** [14]. We presumed that the observed regio- and steroselectivity results from simultaneous coordination of lithium ion at the oxygen atom in the oxirane ring and nitrogen atom in the piperidine ring. Such coordination is possible for *N*-alkylpiperidines but is hardly probable for *N*-acyl and *N*-carbamoyl derivatives in which the basicity of the piperidine nitrogen atom is reduced due to the presence of electron-withdrawing substituent. To verify this assumption we performed *ab initio* quantum-chemical calculations (HF/6-31G**) for the conformational equilibrium involving epoxide **IV**, as well as for the complex of **IV** with lithium cation (complex **G**; Scheme 4). Two stable conformations of molecule **IV** were found: the first of these is characterized by *syn* orientation of the piperidine nitrogen atom and oxygen atom in the oxirane ring (*syn*-**A**), while the corresponding atoms in the other conformer (*anti*-**B**) are arranged *anti*. The latter (**B**) is more stable than the former (**A**) by 1.6 kcal/mol.

The C^4–O bond in *syn*-**A** is slightly longer than C^3–O; the opposite pattern is observed for *anti*-**B**. This means that the predominant conformer *anti*-**B** should react with nucleophiles preferentially at the C^3 atom

Scheme 3.



XXV **XXIIIa**, **XXIIIb** **XXVIa** **XXVIb**

Table 2. Rearrangement of an equimolar mixture of isomeric epoxypiperidines **XXIIIa** and **XXIIIb** (^{1}H NMR data)

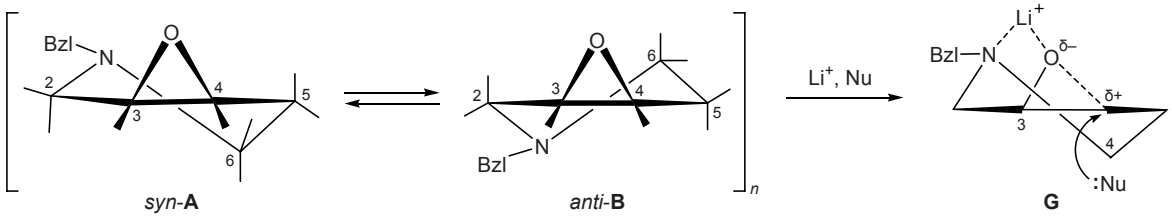
Run no.	LDA, equiv	Reaction time, h	Temperature, °C	Ratio **XXIIIa**:**XXVIa**:**XXVIb**	Overall yield, %
1	2.2	2.5	10	0.9:1:1	65
2	2.2	5	10	0.7:1:1	20
3	1.1	5	–10	0.9:0:1	90

and that the C^4 atom should be more reactive in minor conformer *syn*-**A**. In the presence of lithium ions the conformational equilibrium shifts toward *syn*-**A** since simultaneous coordination of lithium ion at the piperidine nitrogen atom and oxirane oxygen atom to form complex **G** is possible only in that structure (Scheme 4). In keeping with the results of calculations of complex **G** derived from *syn*-**A**, both C^4–O (1.437 Å) and C^3–O bonds (1.427 Å) in the complex are considerably longer than in the initial epoxy derivative **IV** (1.406 and 1.397 Å, respectively, in *syn*-**A**). Cleavage of the longer C^4–O bond by the action of nucleophiles should occur more readily than cleavage of the shorter (and hence stronger) C^3–O bond. This conclusion is very consistent with the experimentally observed selectivity of the reaction of 3,4-epoxypiperidines with amines. We also showed that the employed calculation procedure appropriately reproduces geometric parameters of molecules under study. For this purpose, conformational equilibria of epoxypiperidine **IV** and its analogs **XXIa**/**XXIb** and **XXVIIa**/**XXVIIb** were examined using ^{1}H and ^{13}C NMR spectroscopy, including double resonance techniques, and the results were compared with the calculated data for conformers of compound **IV**.

The ^{1}H NMR spectral patterns were fairly complex, especially for stereoisomeric 6-benzyloxymethyl- and 6-methyl-3,4-epoxy derivatives **XXIIIa**/**XXIIIb** and **XXVIIa**/**XXVIIb**; therefore, double resonance experiments were performed to determine predominant conformations and orientations of the oxirane ring and substituents in molecules **IV**, **V**, **XXIIIa**, **XXIIIb**, **XXVIIa**, and **XXVIIb**. In keeping with the geminal ($^2J_{5\text{-}ax,5\text{-}eq}$ = 14.6 Hz) and vicinal coupling constants ($^3J_{5\text{-}ax,6\text{-}ax}$ = 9.4, $^3J_{5\text{-}ax,4}$ = 2.6 Hz) in the ^{1}H NMR spectrum of **IV**, the multiplet signal at δ 1.99 ppm was assigned to the axial proton on C^5. On the basis of these data we assigned all signals from protons in the piperidine ring (Table 3). It should be noted that two sets of signals with equal intensities were observed in the spectra of 6-substituted 3,4-epoxy derivatives **XXIIIa**/**XXIIIb** and **XXVIIa**/**XXVIIb**, indicating the presence of *cis* and *trans* isomers. Because of strong overlap, only the chemical shifts of protons in the 6-methyl group and 1-benzyl substituent and of 5-H in isomeric epoxy derivatives **XXVIIa** and **XXVIIb** were determined.

To assign stereoisomers **XXIIIa**, **XXIIIb**, **XXVIIa**, and **XXVIIb** to *cis* and *trans* series on the basis of the $^3J_{5\text{-}ax,6}$ and $^3J_{5\text{-}eq,6}$ values, it was necessary to determine orientation of the oxirane ring and substituent on C^6 (Table 4). The coupling constants $^3J_{5\text{-}ax,6}$ for isomeric epoxides **XXIIIa**/**XXIIIb** and **XXVIIa**/**XXVIIb** are fairly similar; they range from 6.6 to 8.2 Hz, which

Scheme 4.



syn-**A** *anti*-**B** **G**

syn-**A** *anti*-**B**

Table 3. Chemical shifts of protons (δ, ppm) in the ^{1}H NMR spectra of epoxypiperidines **IV**, **XXIIIa**, **XXIIIb**, **XXVIIa**, and **XXVIIb** in $CDCl_3$

Compound no.	CH_3	2-H_{ax}	2-H_{eq}	3-H	4-H	5-H_{ax}	5-H_{eq}	6-H_{ax}	6-H_{eq}
IV	–	2.67	3.01	3.18–3.23[a]		1.99	2.03	2.19	2.32
XXIIIa	–	2.83	3.02	3.12	3.24	2.00–2.11[b]		2.92	–
XXIIIb	–	2.77	3.04	3.10	3.27	1.95		2.06	2.79
XXVIIa	1.08[c]; 1.10[c]	2.83	3.02	3.12	3.24	1.85		2.09	
XXVIIb		2.77	3.04	3.10	3.27	1.71		2.00	2.79

[a] Overlapping signals,
[b] *AB* spin system.
[c] Similar chemical shifts of protons in the pseudoaxial and pseudoequatorial positions.

Table 4. Coupling constants *J* (Hz) in the ^{1}H NMR spectra of epoxypiperidines **IV**, **XXIIIa**, **XXIIIb**, **XXVIIa**, and **XXVIIb**

Coupling constant	**IV**	**XXIIIa**	**XXIIIb**	**XXVIIa**	**XXVIIb**
$^3J_{5\text{-}ax,6}$		7.6	8.2	6.6	7.6
$^3J_{5\text{-}eq,6}$		5.3	–[a]	5.8	–[a]
$^3J_{2\text{-}ax,3}$	0	–[a]	–[a]	3.8	0
$^3J_{2\text{-}eq,3}$	4.1	–[a]	–[a]	0	3.9
$^3J_{4,5\text{-}ax}$	2.6	0	3.1	1.3	3.5
$^3J_{4,5\text{-}eq}$	1.5	4.4	0	3.0	0

[a] The coupling constant was not determined because of poor resolution of the multiplet signal.

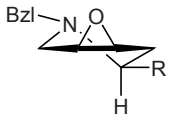
corresponds to pseudoaxial orientation of 6-H. Therefore, the substituent on C^6 in **XXIIIa**/**XXIIIb** and **XXVIIa**/**XXVIIb** occupies pseudoequatorial position. This is possible only for the *syn* conformer of *cis* isomers **XXIIIa** and **XXVIIa** and only for the *anti* conformer of *trans* isomers **XXIIIb** and **XXVIIb**.

We also determined vicinal coupling constants for protons on C^3 and C^4, on the one hand, and those on C^2 and C^5, on the other (Table 4). Analysis of their values (^3J = 0–4.7 Hz) revealed some general relations. In particular, epoxy derivatives **IV**, **V**, **XXIIIb**, and **XXVIIb** are characterized by the following coupling constants: $^3J_{2\text{-}ax,3} \approx 0.0$ Hz $< {}^3J_{2\text{-}eq,3} \approx 3.9$– 4.7 Hz; $^3J_{4,5\text{-}ax} \approx 2.6$–3.5 Hz $> {}^3J_{4,5\text{-}eq} \approx 0.0$–1.7 Hz. The opposite pattern is observed for isomers **XXIIIa** and **XXVIIa**: $^3J_{2\text{-}ax,3} \approx 3.8$ Hz $> {}^3J_{2\text{-}eq,3} \approx 0.0$ Hz; $^3J_{4,5\text{-}ax} \approx$ 0.0–1.3 Hz $< {}^3J_{4,5\text{-}eq} \approx 3.0$–4.4 Hz. These data suggest that *cis* isomers **XXIIIa** and **XXVIIa** and *trans* isomers **XXIIIb** and **XXVIIb** have different conformations, *syn*-**A** and *anti*-**B**, respectively. We then calculated the vicinal coupling constants $^3J_{2,3}$ for *syn*-**A** and *anti*-**B**; the results showed that $^3J_{2\text{-}ax,3} < {}^3J_{2\text{-}eq,3}$ for *anti*-**B** and that $^3J_{2\text{-}ax,3} > {}^3J_{2\text{-}eq,3}$ for *syn*-**A**, which is very consistent with the corresponding experimental coupling constants (Table 5).

Table 5. Calculated and experimental coupling constants for *syn* and *anti* conformers (**A**, **B**) of epoxypiperidine **IV**

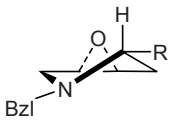
Compound no.	$^3J_{2\text{-}ax,3}$	$^3J_{2\text{-}eq,3}$
anti-**B**-**IV**	1.4[a]	6.0[a]
syn-**A**-**IV**	3.6[a]	2.1[a]
IV, **V**, **XXIIIb**, **XXVIIb**	0.0	3.9–4.7
XXIIIa, **XXVIIa**	3.8	0.0

[a] Calculated values.



syn-**A**

cis-**XXIIIa**, *cis*-**XXVIIa**



anti-**B**

trans-**XXIIIb**, *trans*-**XXVIIb**

Comparison of the experimental and calculated data led us to conclude that 3,4-epoxypiperidines **IV**, **V**, **XXIIIb**, and **XXVIIb** adopt conformation **B** with *anti* orientation of the oxirane oxygen and piperidine nitrogen atoms and that epoxy derivatives **XXIIIa** and **XXVIIa** are *syn* conformers (half-*chair*). As shown above, the substituent on C^6 in **XXIIIa**, **XXIIIb**, **XXVIIa**, and **XXVIIb** occupies pseudoequatorial position; therefore, epoxides **XXIIIb** and **XXVIIb**

(*anti*-**B**) are in fact *trans* isomers. In contrast, *syn* conformers of **XXIIIa** and **XXVIIa** (*cis* orientation of the substituents) belong to the *cis* series. Thus both *syn* and *anti* conformers of isomeric epoxypiperidines were identified. Extension and polarization of the C^4–O bond and a considerable positive charge on the C^4 atom (0.063 on C^4 against 0.029 on C^3) in the *syn* conformer of lithium complex **G** are likely to be the main factors responsible for strictly selective nucleophilic attack on the C^4 atom of the piperidine ring in 3,4-epoxypiperidines.

We can conclude that the formation of complex **G** is preceded by shift of conformational equilibrium of 1-benzyl-3,4-epoxypiperidines from energetically more favorable *anti* conformer (*anti*-**B**) toward *syn* conformer (*syn*-**A**). The regio and stereoselectivity in opening of the oxirane ring of 1-benzyl-3,4-epoxypiperidines by the action of nitrogen, carbon, and sulfur-centered nucleophiles in the presence of lithium perchlorate is determined by coordination of lithium ion simultaneously at the nitrogen atom in the piperidine ring and oxygen atom in the oxirane ring in the *syn* conformer. The results of our study allowed us to identify preferential conformations of 3,4-epoxypiperidines **IV**, **V**, **XXIIIa**, **XXIIIb**, **XXVIIa**, and **XXVIIb** on the basis of the experimental and calculated coupling constants, and criteria were proposed for the assignment of epoxides **XXIIIa**/**XXIIIb** and **XXVIIa**/**XXVIIb** to the *cis* and *trans* series.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR-400 spectrometer (400 MHz for ^{1}H) using chloroform-*d* as solvent and tetramethylsilane as internal reference. The mass spectra (electron impact, 70 eV) were obtained on a Finnigan SSQ7000 GC–MS system (DB5 capillary column, 30 m). Thin-layer chromatography was performed using silica gel plates (Merck), and Silica gel 60 (Merck) was used for column chromatography.

***trans*-1-Benzyl-4-benzylaminopiperidin-3-ol dihydrochloride (VI).** Anhydrous lithium perchlorate, 0.280 g (2.65 mmol), was added to a solution of 0.500 g (2.65 mmol) of 1-benzyl-3,4-epoxypiperidine (**IV**) in 5 ml of anhydrous acetonitrile, the mixture was stirred until it became homogeneous, 0.285 g (2.65 mmol) of benzylamine was added, and the mixture was stirred for 24 h at room temperature. The progress of the reaction was monitored by TLC following disappearance of the initial epoxy derivative. The mixture was treated with 3 ml of water, the solvent (acetonitrile) was distilled off under reduced pressure, and the resulting dispersion was extracted with methylene chloride (5×2 ml). The extracts were combined, dried over anhydrous sodium sulfate, and evaporated, the residue (0.750 g) was dissolved in 10 ml of anhydrous ethanol, and a saturated solution of hydrogen chloride in anhydrous ethanol was added to pH 4. The solvent was removed on a rotary evaporator, and the product was dried under reduced pressure over alkali and phosphoric anhydride, recrystallized from anhydrous ethanol, washed with diethyl ether, and dried under reduced pressure. Yield 0.840 g (86%), colorless crystals, mp 213–214°C (decomp., from EtOH). Found, %: C 61.84; H 7.25; N 7.38. $C_{17}H_{26}Cl_2N_2O$. Calculated, %: C 61.79; H 7.10; N 7.58.

***trans*-1-Benzyl-4-benzylaminopiperidin-3-ol (**free base**).** ^{1}H NMR spectrum, δ, ppm: 1.33 m (1H, 5-H_{ax}, $^2J_{5\text{-}ax,5\text{-}eq}$ = 12.9, $^3J_{5\text{-}ax,6\text{-}ax}$ = 12.9, $^3J_{5\text{-}ax,6\text{-}eq}$ = 4.5, $^3J_{5\text{-}ax,4\text{-}ax}$ = 10.9 Hz), 1.90 t (1H, 2-H_{ax}, $^3J_{2\text{-}ax,2\text{-}eq}$ = 10.5, $^2J_{2\text{-}ax,3\text{-}ax}$ = 9.7 Hz), 1.95–2.03 m (2H, 6-H_{ax}, 5-H_{eq}), 2.03 d.d.d (1H, 4-H_{ax}, $^3J_{4\text{-}ax,5\text{-}ax}$ 10.9, $^3J_{4\text{-}ax,3\text{-}ax}$ = 9.1, $^3J_{4\text{-}ax,5\text{-}eq}$ = 4.1 Hz), 2.60 br.s (2H, 3-OH, 4-NH), 2.80 m (1H, 6-H_{eq}, $^2J_{6\text{-}eq,6\text{-}ax}$ = 10.7 Hz), 2.98 d.d.d (1H, 2-H_{eq}, $^2J_{2\text{-}eq,2\text{-}ax}$ = 10.5, $^3J_{2\text{-}eq,3\text{-}ax}$ = 4.4, $^4J_{2\text{-}eq,6\text{-}eq}$ = 1.8 Hz), 3.43 d.t (1H, 3-H_{ax}, $^3J_{3\text{-}ax,4\text{-}ax}$ = 9.1, $^3J_{3\text{-}ax,2\text{-}ax}$ = 9.7, $^3J_{3\text{-}ax,2\text{-}eq}$ = 4.4 Hz), 3.49 (2H, PhC**H**$_2$, *AB* system, ^2J = 13.2 Hz), 3.65 d (1H, PhC**H**$_2$, ^2J = 13.2 Hz), 3.87 d (1H, PhC**H**$_2$, ^2J = 13.2 Hz), 7.21–7.32 m (10H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 29.28 (C^5); 50.66; 52.03, 58.54, 61.01, 62.54 (C^2, C^4, C^6, Ph**C**H_2); 70.66 (C^3); 126.98 (2C), 128.02 (2C), 128.12 (2C), 128.37 (2C), 129.03 (2C), 137.99, 140.18 (C_{arom}).

Compounds **VII**–**XII**, **XIV**–**XVI**, **XVIII**–**XXII**, and **XXIV** were synthesized in a similar way.

***trans*-1-Benzyl-4-ethylaminopiperidin-3-ol dihydrochloride (VII)** was synthesized from 0.500 g (2.65 mmol) of compound **IV** and 0.120 g (2.65 mmol) of ethylamine (reaction time 24 h). Yield 0.550 g (89%), colorless crystals, mp 233–234°C (from EtOH). Found, %: C 54.90; H 7.93; N 9.04. $C_{14}H_{24}Cl_2N_2O$. Calculated, %: C 54.73; H 7.87; N 9.12.

***trans*-1-Benzyl-4-ethylaminopiperidin-3-ol (**free base**).** ^{1}H NMR spectrum, δ, ppm: 1.10 t (3H, CH_3, ^3J = 6.5 Hz), 1.56 d.q (1H, 5-H_{ax}, $^2J_{5\text{-}ax,5\text{-}eq}$ = 12.3, $^3J_{5\text{-}ax,6\text{-}ax}$ = 11.6, $^3J_{5\text{-}ax,6\text{-}eq}$ = 3.9, $^3J_{5\text{-}ax,4\text{-}ax}$ = 12.1 Hz), 1.67 m (1H, 5-H_{eq}, $^2J_{5\text{-}eq,5\text{-}ax}$ = 12.3 Hz), 1.93 t (1H, 2-H_{ax}, $^2J_{2\text{-}ax,2\text{-}eq}$ = 10.1, $^3J_{2\text{-}ax,3\text{-}ax}$ = 9.9 Hz), 2.00 d.t (1H, 6-H_{ax}, $^2J_{6\text{-}eq,6\text{-}ax}$ = 11.4, $^3J_{6\text{-}ax,5\text{-}ax}$ = 11.6, $^3J_{6\text{-}ax,5\text{-}eq}$ = 2.4 Hz), 2.20 d.d.d (1H, 4-H_{ax}, $^3J_{4\text{-}ax,5\text{-}ax}$ = 12.1,

$^3J_{4\text{-}ax,3\text{-}ax}$ = 8.9, $^3J_{4\text{-}ax,5\text{-}ax}$ = 3.6 Hz), 2.45 m (1H, C**H**$_2$CH$_3$), 2.72 m (1H, C**H**$_2$CH$_3$), 2.87 m (1H, 6-H$_{eq}$, $^2J_{6\text{-}eq,6\text{-}ax}$ = 11.4 Hz), 3.18 d.d.d (1H, 2-H$_{eq}$, $^2J_{2\text{-}eq,2\text{-}ax}$ = 10.1, $^3J_{2\text{-}eq,3\text{-}ax}$ = 4.3, $^4J_{2\text{-}eq,6\text{-}eq}$ = 1.0 Hz), 3.30 br.s (2H, OH, NH), 3.55 (2H, PhC**H**$_2$, *AB* system, ^2J = 13.2 Hz), 3.31 d.t (1H, 3-H$_{ax}$, $^3J_{3\text{-}ax,4\text{-}ax}$ = 8.9, $^3J_{3\text{-}ax,2\text{-}ax}$ = 9.9, $^3J_{3\text{-}ax,2\text{-}eq}$ = 4.4 Hz), 7.21–7.34 m (5H, Ph).

***trans*-1-Benzyl-4-cyclohexylmethylpiperidin-3-ol dihydrochloride (VIII)** was synthesized from 0.500 g (2.65 mmol) of compound **IV** and 0.300 g (2.65 mmol) of cyclohexylmethanamine (reaction time 24 h). Yield 0.750 g (94%), colorless crystals, mp 258–259°C (decomp., EtOH). Found, %: C 61.05; H 8.50; N 7.62. $C_{19}H_{32}Cl_2N_2O$. Calculated, %: C 60.79; H 8.59; N 7.46.

***trans*-1-Benzyl-4-cyclohexylmethylpiperidin-3-ol (**free base**).** ^{1}H NMR spectrum, δ, ppm: 1.06–1.14 m (4H, CH$_2$, cyclohexyl), 1.2–1.5 m (8H, 5-H$_{ax}$, CH$_2$, CH, cyclohexyl), 1.70 m (1H, 5-H$_{eq}$, $^2J_{5\text{-}eq,5\text{-}ax}$ = 11.9 Hz), 1.90 t (1H, 2-H$_{ax}$, $^2J_{2\text{-}ax,2\text{-}eq}$ = 10.0, $^3J_{2\text{-}ax,3\text{-}ax}$ = 9.8 Hz), 2.00 d.t (1H, 6-H$_{ax}$, $^2J_{6\text{-}eq,6\text{-}ax}$ = 11.3, $^3J_{6\text{-}ax,5\text{-}ax}$ = 11.5, $^3J_{6\text{-}ax,5\text{-}eq}$ = 2.6 Hz), 2.21 d.d.d (1H, 6-H$_{ax}$, $^3J_{4\text{-}ax,5\text{-}ax}$ = 11.9, $^3J_{4\text{-}ax,3\text{-}ax}$ = 9.1, $^3J_{4\text{-}ax,5\text{-}eq}$ = 3.7 Hz), 2.40–2.55 m (3H, 3-H$_{eq}$, NHC**H**$_2$), 3.15 m (1H, 2-H$_{eq}$, $^2J_{2\text{-}eq,2\text{-}ax}$ = 10.0 Hz), 3.37 d.t (1H, 3-H$_{ax}$, $^3J_{3\text{-}ax,4\text{-}ax}$ = 9.1, $^3J_{3\text{-}ax,2\text{-}ax}$ = 9.8, $^3J_{3\text{-}ax,2\text{-}eq}$ = 3.9 Hz), 3.55 (2H, PhC**H**$_2$, *AB* system, ^2J = 13.4 Hz), 3.64 br.s (2H, OH, NH), 7.20–7.33 m (5H, Ph).

***trans*-1-Benzyl-4-morpholinopiperidin-3-ol dihydrochloride (IX)** was synthesized from 0.500 g (2.65 mmol) of compound **IV** and 0.230 g (2.65 mmol) of morpholine (reaction time 48 h). Yield 0.810 g (88%), colorless crystals, mp 241–242°C (decomp., from EtOH). Found, %: C 54.91; H 7.94; N 7.68. $C_{16}H_{26}Cl_2N_2O_2$. Calculated, %: C 55.02; H 7.50; N 8.02.

***trans*-1-Benzyl-4-morpholinopiperidin-3-ol (**free base**).** ^{1}H NMR spectrum, δ, ppm: 1.54 d.q (1H, 5-H$_{ax}$, $^2J_{5\text{-}ax,5\text{-}eq}$ = 12.5, $^3J_{5\text{-}ax,6\text{-}ax}$ = 11.9, $^3J_{5\text{-}ax,6\text{-}eq}$ = 4.1, $^3J_{5\text{-}ax,4\text{-}ax}$ = 12.1 Hz), 1.72 m (1H, 5-H$_{eq}$, $^2J_{5\text{-}eq,5\text{-}ax}$ = 12.5 Hz), 1.89 t (1H, 2-H$_{ax}$, $^2J_{2\text{-}ax,2\text{-}eq}$ = 10.4, $^3J_{2\text{-}ax,3\text{-}ax}$ = 9.9 Hz), 1.98 d.t (1H, 6-H$_{ax}$, $^2J_{6\text{-}eq,6\text{-}ax}$ = 11.5, $^3J_{6\text{-}ax,5\text{-}ax}$ = 11.9, $^3J_{6\text{-}ax,5\text{-}eq}$ = 2.5 Hz), 2.18 d.d.d (1H, 4-H$_{ax}$, $^3J_{4\text{-}ax,5\text{-}ax}$ = 12.1, $^3J_{4\text{-}ax,3\text{-}ax}$ = 9.8, $^3J_{4\text{-}ax,5\text{-}eq}$ = 3.8 Hz), 2.43 m (2H, 2′-H, 6′-H), 2.72 m (2H, 2′-H, 6′-H), 2.94 m (1H, 6-H$_{eq}$, $^2J_{6\text{-}eq,6\text{-}ax}$ = 11.5 Hz), 3.21 d.d.d (1H, 2-H$_{eq}$, $^2J_{2\text{-}eq,2\text{-}ax}$ = 10.4, $^3J_{2\text{-}eq,3\text{-}ax}$ = 4.6, $^4J_{2\text{-}eq,6\text{-}eq}$ = 2.0 Hz), 3.43 br.s (1H, 3-OH), 3.54 (2H, PhC**H**$_2$, *AB* system, ^2J = 13.1 Hz), 3.59 d.t (1H, 3-H$_{ax}$, $^3J_{3\text{-}ax,4\text{-}ax}$ = 9.8, $^3J_{3\text{-}ax,2\text{-}ax}$ = 9.9, $^3J_{3\text{-}ax,2\text{-}eq}$ = 4.6 Hz), 3.71 m (4H, 3′-H, 5′-H), 7.21–7.34 m (5H, Ph). ^{13}C NMR spectrum, δ_C, ppm: 21.52 (C^5); 48.84 (C$^{2'}$, C$^{6'}$); 52.81 (C^6); 58.72, 62.62, 65.81 (C^2, C^4, PhCH$_2$); 67.43 (C$^{3'}$, C$^{5'}$); 69.37 (C^3); 127.06, 128.17 (2C), 129.06 (2C), 137.94 (C$_{arom}$).

***trans*-1-Benzyl-4-(1-methylpiperazin-4-yl)piperidin-3-ol trihydrochloride (X)** was synthesized from 0.500 g (2.65 mmol) of compound **IV** and 0.265 g (2.65 mmol) of *N*-methylpiperazine (reaction time 48 h). Yield 0.875 g (83%), colorless crystals, mp 270–271°C (decomp., EtOH). Found, %: C 51.18; H 7.35; N 10.25. $C_{17}H_{30}Cl_3N_3O$. Calculated, %: C 51.02; H 7.58; N 10.54.

***trans*-1-Benzyl-4-(1-methylpiperazin-4-yl)piperidin-3-ol (**free base**).** ^{1}H NMR spectrum, δ, ppm: 1.53 d.q (1H, 5-H$_{ax}$, $^2J_{5\text{-}ax,5\text{-}eq}$ = 12.5, $^3J_{5\text{-}ax,6\text{-}ax}$ = 11.8, $^3J_{5\text{-}ax,6\text{-}eq}$ = 4.0, $^3J_{5\text{-}ax,4\text{-}ax}$ = 12.4 Hz), 1.71 m (1H, 5-H$_{eq}$, $^2J_{5\text{-}eq,5\text{-}ax}$ = 12.5 Hz), 1.88 t (1H, 2-H$_{ax}$, $^3J_{2\text{-}ax,2\text{-}eq}$ = 10.2, $^2J_{2\text{-}ax,3\text{-}ax}$ = 9.7 Hz), 1.97 d.t (1H, 6-H$_{ax}$, $^2J_{6\text{-}eq,6\text{-}ax}$ = 11.2, $^3J_{6\text{-}ax,5\text{-}ax}$ = 11.8, $^3J_{6\text{-}ax,5\text{-}eq}$ = 2.4 Hz), 2.20 d.d.d (1H, 4-H$_{ax}$, $^3J_{4\text{-}ax,5\text{-}ax}$ = 12.4, $^3J_{4\text{-}ax,3\text{-}ax}$ = 10.0, $^3J_{4\text{-}ax,5\text{-}eq}$ = 4.0 Hz), 2.28 s (3H, NCH$_3$), 2.35–2.51 m (6H, CH$_2$, piperazine), 2.72–2.80 m (2H, CH$_2$, piperazine), 2.92 m (1H, 6-H$_{eq}$, $^2J_{6\text{-}eq,6\text{-}ax}$ = 11.2 Hz), 3.21 d.d.d (1H, 2-H$_{eq}$, $^2J_{2\text{-}eq,2\text{-}ax}$ = 10.2, $^3J_{2\text{-}eq,3\text{-}ax}$ = 4.6, $^4J_{2\text{-}eq,6\text{-}eq}$ = 1.8 Hz), 3.47 br.s (1H, 3-OH), 3.53 (2H, PhC**H**$_2$, *AB* system, ^2J = 13.4 Hz), 3.58 d.t (1H, 3-H$_{ax}$, $^3J_{3\text{-}ax,4\text{-}ax}$ = 10.0, $^3J_{3\text{-}ax,2\text{-}ax}$ = 9.7, $^3J_{3\text{-}ax,2\text{-}eq}$ = 4.6 Hz), 7.21–7.32 m (5H, Ph). ^{13}C NMR spectrum, δ_C, ppm: 21.52 (C^5), 46.01 (CH$_3$); 48.30 br (C$^{2'}$, C$^{6'}$); 52.92 (C^6); 55.62 (C$^{3'}$, C$^{5'}$); 58.82, 62.64, 65.95 (C^2, C^4, PhCH$_2$); 68.94 (C^3); 127.01, 128.14 (2C), 129.05 (2C), 138.05 (C$_{arom}$).

***trans*-1-Benzyl-4-[4-(pyridin-2-yl)piperazin-1-yl]-piperidin-3-ol (XI)** was synthesized from 0.500 g (2.65 mmol) of compound **IV** and 0.430 g (2.65 mmol) of *N*-(pyridin-2-yl)piperazine (reaction time 48 h). The precipitate of free base **XI** was filtered off, washed with water (2×5 ml), dried under reduced pressure, and recrystallized from ethanol. Yield 0.880 g (95%), colorless crystals, mp 134–135°C (from EtOH). ^{1}H NMR spectrum, δ, ppm: 1.56 d.q (1H, 5-H$_{ax}$, $^2J_{5\text{-}ax,5\text{-}eq}$ = 12.5, $^3J_{5\text{-}ax,6\text{-}ax}$ = 12.0, $^3J_{5\text{-}ax,6\text{-}eq}$ = 4.1, $^3J_{5\text{-}ax,4\text{-}ax}$ = 12.1 Hz), 1.72 m (1H, 5-H$_{eq}$, $^2J_{5\text{-}eq,5\text{-}ax}$ = 12.5 Hz), 1.92 t (1H, 2-H$_{ax}$, $^3J_{2\text{-}ax,2\text{-}eq}$ = 10.2, $^2J_{2\text{-}ax,3\text{-}ax}$ = 9.9 Hz), 2.01 d.t (1H, 6-H$_{ax}$, $^2J_{6\text{-}eq,6\text{-}ax}$ = 11.5, $^3J_{6\text{-}ax,5\text{-}ax}$ = 12.0, $^3J_{6\text{-}ax,5\text{-}eq}$ = 2.5 Hz), 2.29 d.d.d (1H, 4-H$_{ax}$, $^3J_{4\text{-}ax,5\text{-}ax}$ = 12.1, $^3J_{4\text{-}ax,3\text{-}ax}$ = 9.9, $^3J_{4\text{-}ax,5\text{-}eq}$ = 3.8 Hz), 2.54 m (2H, 2′-H, 6′-H), 2.85 m (2H, 2′-H, 6′-H), 2.95 m (1H, 6-H$_{eq}$, $^2J_{6\text{-}eq,6\text{-}ax}$ = 11.5 Hz), 3.24 d.d.d (1H, 2-H$_{eq}$, $^2J_{2\text{-}eq,2\text{-}ax}$ = 10.2, $^3J_{2\text{-}eq,3\text{-}ax}$ = 4.4, $^4J_{2\text{-}eq,6\text{-}eq}$ = 2.0 Hz), 3.47–3.61 m (7H, 3′-H, 5′-H, 3-OH, PhC**H**$_2$),

3.66 d.t (1H, 3-H$_{ax}$, $^3J_{3\text{-}ax,4\text{-}ax}$ = 9.9, $^3J_{3\text{-}ax,2\text{-}ax}$ = 9.9, $^3J_{3\text{-}ax,2\text{-}eq}$ = 4.4 Hz), 6.61 d.d (1H, 5″-H, $^3J_{5'',4''}$ = 7.1, $^3J_{5'',6''}$ = 5.0 Hz), 6.63 d (1H, 3″-H, $^3J_{3'',4''}$ = 9.0 Hz), 7.21–7.34 m (5H, Ph), 7.47 d.d.d (1H, 4″-H, $^3J_{4'',5''}$ = 7.1, $^3J_{4'',3''}$ = 9.0, $^4J_{4'',6''}$ = 2.0 Hz), 8.18 m (1H, 6″-H, $^3J_{6'',5''}$ = 5.0, $^4J_{6'',4''}$ = 2.0 Hz). ^{13}C NMR spectrum, δ_C, ppm: 21.57 (C^5); 45.72 and 48.32 (piperazine); 52.18, 58.74, 62.63, 65.99 (C^2, C^4, C^6, Ph**C**H$_2$); 69.19 (C^3); 107.02, 113.36 (C$_5$H$_4$N); 127.13, 128.02 (2C), 129.11 (2C) (C$_{arom}$); 137.43 (C$_5$H$_4$N); 137.83 (Ph); 147.83, 159.43 (C$_5$H$_4$N). Found, %: C 71.50; H 7.89; N 15.70. $C_{21}H_{28}N_4O$. Calculated, %: C 71.56; H 8.01; N 15.89.

***trans*-4-(Azepan-1-yl)-1-benzylpiperidin-3-ol dihydrochloride (XII)** was synthesized from 0.500 g (2.65 mmol) of compound **IV** and 0.260 g (2.65 mmol) of azepane (reaction time 48 h). Yield 0.850 g (89%), colorless crystals, mp 236–238°C (decomp., from EtOH). Found, %: C 59.75; H 8.45; N 7.63. $C_{18}H_{30}Cl_2N_2O$. Calculated, %: C 59.83; H 7.37; N 7.75.

***trans*-4-(Azepan-1-yl)-1-benzylpiperidin-3-ol (**free base**).** ^{1}H NMR spectrum, δ, ppm: 1.46–1.71 m (10H, 5-H$_{ax}$, 5-H$_{eq}$, CH$_2$, azepane), 1.85 t (1H, 2-H$_{ax}$, $^2J_{2\text{-}ax,2\text{-}eq}$ = 10.1, $^3J_{2\text{-}ax,3\text{-}ax}$ = 9.9 Hz), 1.97 d.t (1H, 6-H$_{ax}$, $^2J_{6\text{-}eq,6\text{-}ax}$ = 11.5, $^3J_{6\text{-}ax,5\text{-}ax}$ = 11.5, $^3J_{6\text{-}ax,5\text{-}eq}$ = 2.8 Hz), 2.21 d.d.d (1H, 4-H$_{ax}$, $^3J_{4\text{-}ax,5\text{-}ax}$ = 12.1, $^3J_{4\text{-}ax,3\text{-}ax}$ = 9.9, $^3J_{4\text{-}ax,5\text{-}eq}$ = 3.9 Hz), 2.44–2.53 m and 2.76–2.84 m (2H each, 2′-H, 7′-H), 2.91 m (1H, 6-H$_{eq}$, $^2J_{6\text{-}eq,6\text{-}ax}$ = 11.5 Hz), 3.21 d.d.d (1H, 2-H$_{eq}$, $^2J_{2\text{-}eq,2\text{-}ax}$ = 10.1, $^3J_{2\text{-}eq,3\text{-}ax}$ = 4.6, $^4J_{2\text{-}eq,6\text{-}eq}$ = 2.0 Hz), 3.49 d.t (1H, 3-H$_{ax}$, $^3J_{3\text{-}ax,4\text{-}ax}$ = 9.9, $^3J_{3\text{-}ax,2\text{-}ax}$ = 9.9, $^3J_{3\text{-}ax,2\text{-}eq}$ = 4.6 Hz), 3.53 (2H, PhC**H**$_2$, *AB* system, ^2J = 13.1 Hz), 3.64 br.s (1H, 3-OH), 7.20–7.33 m (5H, Ph). ^{13}C NMR spectrum, δ_C, ppm: 22.05 (C^5); 25.81 (2C) and 29.79 (2C) (CH$_2$, azepane); 51.18 (2C, CH$_2$, azepane); 53.14, 58.84, 62.70, 66.94 (C^2, C^4, C^6, Ph**C**H$_2$); 70.74 (C^3); 126.97, 128.12 (2C), 129.05 (2C), 138.16 (C$_{arom}$).

***trans*-1-Benzyl-4-diethylaminopiperidin-3-ol dihydrobromide (XIV)** was synthesized from 0.500 g (2.65 mmol) of compound **IV** and 0.190 g (2.65 mmol) of diethylamine (reaction time 72 h). Yield 0.580 g (52%), colorless crystals, mp 239–240°C (from EtOH). Found, %: C 45.28; H 7.01; N 6.72. $C_{16}H_{28}Br_2N_2O$. Calculated, %: C 45.30; H 6.65; N 6.60.

***trans*-1-Benzyl-4-diethylaminopiperidin-3-ol (**free base**).** ^{1}H NMR spectrum, δ, ppm: 1.03 t (6H, CH$_3$, ^3J = 7.2 Hz), 1.52 d.q (1H, 5-H$_{ax}$, $^2J_{5\text{-}ax,5\text{-}eq}$ = 12.5, $^3J_{5\text{-}ax,6\text{-}ax}$ = 12.0, $^3J_{5\text{-}ax,6\text{-}eq}$ = 4.1, $^3J_{5\text{-}ax,4\text{-}ax}$ = 12.3 Hz), 1.65 m (1H, 5-H$_{eq}$, $^2J_{5\text{-}eq,5\text{-}ax}$ = 12.5 Hz), 1.87 t (1H, 2-H$_{ax}$, $^3J_{2\text{-}ax,2\text{-}eq}$ = 10.3, $^2J_{2\text{-}ax,3\text{-}ax}$ = 9.7 Hz), 1.97 d.t (1H, 6-H$_{ax}$, $^2J_{6\text{-}eq,6\text{-}ax}$ = 11.4, $^3J_{6\text{-}ax,5\text{-}ax}$ = 12.0, $^3J_{6\text{-}ax,5\text{-}eq}$ = 2.6 Hz), 2.28 d.d.d (1H, 4-H$_{ax}$, $^3J_{4\text{-}ax,5\text{-}ax}$ = 12.3, $^3J_{4\text{-}ax,3\text{-}ax}$ = 9.8, $^3J_{4\text{-}ax,5\text{-}eq}$ = 4.1 Hz), 2.37 m (2H, CH$_3$C**H**$_2$, ^2J = 13.8, ^3J = 7.2 Hz), 2.65 m (2H, CH$_3$C**H**$_2$, ^2J = 13.8, ^3J = 7.2 Hz), 2.91 m (1H, 6-H$_{eq}$, $^2J_{6\text{-}eq,6\text{-}ax}$ = 11.4 Hz), 3.22 d.d.d (1H, 2-H$_{eq}$, $^2J_{2\text{-}eq,2\text{-}ax}$ = 10.3, $^3J_{2\text{-}eq,3\text{-}ax}$ = 4.4, $^4J_{2\text{-}eq,6\text{-}eq}$ = 2.1 Hz), 3.51 d.t (1H, 3-H$_{ax}$, $^3J_{3\text{-}ax,4\text{-}ax}$ = 9.8, $^3J_{3\text{-}ax,2\text{-}ax}$ = 9.7, $^3J_{3\text{-}ax,2\text{-}eq}$ = 4.4 Hz), 3.54 (2H, PhC**H**$_2$, *AB* system, ^2J = 13.2 Hz), 3.58 br.s (1H, 3-OH), 7.21–7.34 m (5H, Ph). ^{13}C NMR spectrum, δ_C, ppm: 14.67 (CH$_3$); 22.29 (C^5); 43.38 (**C**H$_2$CH$_3$); 53.19, 58.88, 62.71, 65.27, 66.46 (C^2, C^3, C^4, C^6, Ph**C**H$_2$); 126.99, 128.13 (2C), 129.07 (2C), 138.07 (C$_{arom}$).

***trans*-1-Benzyl-4-phenylaminopiperidin-3-ol dihydrochloride (XV)** was synthesized from 0.500 g (2.65 mmol) of compound **IV** and 0.250 g (2.65 mmol) of aniline (reaction time 24 h). Yield 0.780 g (83%), colorless crystals, mp 224–225°C (from EtOH). Found, %: C 60.88; H 7.01; N 7.80. $C_{16}H_{24}Cl_2N_2O$. Calculated, %: C 60.85; H 6.81; N 7.88.

***trans*-1-Benzyl-4-phenylaminopiperidin-3-ol (**free base**).** ^{1}H NMR spectrum, δ, ppm: 1.40 m (1H, 5-H$_{ax}$, $^2J_{5\text{-}ax,5\text{-}eq}$ = 13.4, $^3J_{5\text{-}ax,6\text{-}ax}$ = 10.3, $^3J_{5\text{-}ax,6\text{-}eq}$ = 3.8, $^3J_{5\text{-}ax,4\text{-}ax}$ = 9.8 Hz), 2.07 m (1H, 5-H$_{eq}$, $^2J_{5\text{-}eq,5\text{-}ax}$ = 13.4 Hz), 2.10–2.20 m (2H, 2-H$_{ax}$, 6-H$_{ax}$), 2.71 m (1H, 6-H$_{eq}$, $^2J_{6\text{-}eq,6\text{-}ax}$ = 11.4 Hz), 3.01 d.d (1H, 2-H$_{eq}$, $^2J_{2\text{-}eq,2\text{-}ax}$ = 10.9, $^3J_{2\text{-}eq,3\text{-}ax}$ = 3.8 Hz), 3.05 br.s (2H, 3-OH, 4-NH), 3.19 d.t (1H, 4-H$_{ax}$, $^3J_{4\text{-}ax,5\text{-}ax}$ = 9.8, $^3J_{4\text{-}ax,3\text{-}ax}$ = 8.2, $^3J_{4\text{-}ax,5\text{-}eq}$ = 4.4 Hz), 3.53 (2H, PhC**H**$_2$, *AB* system, ^2J = 13.2 Hz), 3.56 d.t (1H, 3-H$_{ax}$, $^3J_{3\text{-}ax,4\text{-}ax}$ = 8.2, $^3J_{3\text{-}ax,2\text{-}ax}$ = 8.2, $^3J_{3\text{-}ax,2\text{-}eq}$ = 3.8 Hz), 6.63–6.68 m (2H, NH**Ph**), 6.71 m (1H, NH**Ph**), 7.15 m (2H, NH**Ph**), 7.22–7.35 m (5H, CH$_2$**Ph**). ^{13}C NMR spectrum, δ_C, ppm: 29.74 (C^5); 51.62, 56.99, 57.91, 62.56 (C^2, C^4, C^6, Ph**C**H$_2$); 70.81 (C^3); 113.88 (2C), 118.09, 127.14, 128.22 (2C), 129.07 (2C), 129.30 (2C), 137.73, 147.34 (C$_{arom}$).

***trans*-1-Benzyl-4-(2-fluorophenylamino)piperidin-3-ol dihydrochloride (XVI)** was synthesized from 0.500 g (2.65 mmol) of compound **IV** and 0.295 g (2.65 mmol) of 2-fluoroaniline (reaction time 72 h). Yield 0.660 g (67%), colorless crystals, mp 181–182°C (from EtOH). Found, %: C 57.87; H 6.20; N 7.48. $C_{16}H_{23}Cl_2FN_2O$. Calculated, %: C 57.92; H 6.21; N 7.50.

***trans*-1-Benzyl-4-(2-fluorophenylamino)piperidin-3-ol (**free base**).** ^{1}H NMR spectrum, δ, ppm: 1.48 m (1H, 5-H$_{ax}$, $^2J_{5\text{-}ax,5\text{-}eq}$ = 13.5, $^3J_{5\text{-}ax,6\text{-}ax}$ = 9.7, $^3J_{5\text{-}ax,6\text{-}eq}$ = 3.8, $^3J_{5\text{-}ax,4\text{-}ax}$ = 9.7 Hz), 2.08 m (1H, 5-H$_{eq}$, $^2J_{5\text{-}eq,5\text{-}ax}$ = 13.5 Hz), 2.17–2.27 m (2H, 2-H$_{ax}$, 6-H$_{ax}$),

2.66–2.75 m (2H, 6-H$_{eq}$, OH), 3.00 d.d (1H, 2-H$_{eq}$, $^2J_{2\text{-}eq,2\text{-}ax}$ = 10.8, $^3J_{2\text{-}eq,3\text{-}ax}$ = 3.8 Hz), 3.25 m (1H, 4-H$_{ax}$), 3.55 (2H, PhC**H**$_2$, *AB* system, ^2J = 13.2 Hz), 3.64 d.t (1H, 3-H$_{ax}$, $^3J_{3\text{-}ax,4\text{-}ax}$ = 7.9, $^3J_{3\text{-}ax,2\text{-}ax}$ = 7.9, $^3J_{3\text{-}ax,2\text{-}eq}$ = 3.8 Hz), 3.72 br.d (1H, NH), 6.61–6.67 m (1H, C$_6$H$_4$), 6.81 d.t (1H, C$_6$H$_4$), 6.93–7.00 m (2H, C$_6$H$_4$), 7.23–7.36 m (5H, Ph).

***trans*-1-Benzyl-4-benzylamino-3-methylpiperidin-3-ol dihydrochloride (XVII)** was synthesized from 0.500 g (2.46 mmol) of compound **V** and 0.260 g (2.46 mmol) of benzylamine (reaction time 72 h). Yield 0.830 g (88%), colorless crystals, mp 221–222°C (decomp., from EtOH). Found, %: C 62.52; H 7.45; N 7.24. $C_{20}H_{28}Cl_2N_2O$. Calculated, %: C 62.66; H 7.36; N 7.31.

***trans*-1-Benzyl-4-benzylamino-3-methylpiperidin-3-ol (**free base**).** ^{1}H NMR spectrum, δ, ppm: 1.22 s (3H, 3-CH$_3$), 1.42 m (1H, 5-H$_{ax}$, $^2J_{5\text{-}ax,5\text{-}eq}$ = 13.8, $^3J_{5\text{-}ax,6\text{-}ax}$ = 8.9, $^3J_{5\text{-}ax,6\text{-}eq}$ = 3.5, $^3J_{5\text{-}ax,4\text{-}ax}$ = 8.8 Hz), 1.97 m (1H, 5-H$_{eq}$, $^2J_{5\text{-}eq,5\text{-}ax}$ = 13.8, $^3J_{5\text{-}eq,6\text{-}ax}$ = 5.7, $^3J_{5\text{-}eq,6\text{-}eq}$ = 4.1, $^3J_{5\text{-}eq,4\text{-}ax}$ = 4.1 Hz), 2.03 d (1H, 2-H$_{ax}$, $^2J_{2\text{-}ax,2\text{-}eq}$ = 10.4 Hz), 2.18 m (1H, 6-H$_{ax}$, $^2J_{6\text{-}eq,6\text{-}ax}$ = 8.9, $^3J_{6\text{-}ax,5\text{-}ax}$ = 8.9 Hz), 2.43 d.d (1H, 4-H$_{ax}$, $^3J_{4\text{-}ax,5\text{-}ax}$ = 8.8, $^3J_{4\text{-}ax,5\text{-}eq}$ = 4.1 Hz), 2.59 br.d (1H, 2-H$_{eq}$, $^2J_{2\text{-}eq,2\text{-}ax}$ = 10.4 Hz), 2.66 m (1H, 6-H$_{eq}$), 3.45 d (1H, PhC**H**$_2$, ^2J = 13.2 Hz), 3.54 d (1H, PhC**H**$_2$, ^2J = 13.2 Hz), 3.68 d (1H, PhC**H**$_2$, ^2J = 13.1 Hz), 3.91 d (1H, PhC**H**$_2$, ^2J = 13.1 Hz), 7.19–7.43 m (10H, Ph).

***trans*-1-Benzyl-3-methyl-4-(pyrrolidin-1-yl)piperidin-3-ol dihydrochloride (XVIII)** was synthesized from 0.500 g (2.46 mmol) of compound **V** and 0.175 g (2.46 mmol) of pyrrolidine (reaction time 4 days). Yield 0.650 g (76%), colorless crystals, mp 170–171°C (from EtOH). Found, %: C 58.84; H 8.25; N 8.25. $C_{17}H_{28}Cl_2N_2O$. Calculated, %: C 58.79; H 8.13; N 8.07.

***trans*-1-Benzyl-3-methyl-4-(pyrrolidin-1-yl)-piperidin-3-ol (**free base**).** ^{1}H NMR spectrum, δ, ppm: 1.31 s (3H, 3-CH$_3$), 1.56 d.q (1H, 5-H$_{ax}$, $^2J_{5\text{-}ax,5\text{-}eq}$ = 12.4, $^3J_{5\text{-}ax,6\text{-}ax}$ = 11.8, $^3J_{5\text{-}ax,6\text{-}eq}$ = 4.3, $^3J_{5\text{-}ax,4\text{-}ax}$ = 11.9 Hz), 1.68–1.77 m (5H, 5-H$_{eq}$, 3′-H, 4′-H), 1.89 d (1H, 2-H$_{ax}$, $^2J_{2\text{-}ax,2\text{-}eq}$ = 10.4 Hz), 2.02 d.t (1H, 6-H$_{ax}$, $^2J_{6\text{-}eq,6\text{-}ax}$ = 11.3, $^3J_{6\text{-}ax,5\text{-}ax}$ = 11.9, $^3J_{6\text{-}ax,5\text{-}eq}$ = 3.0 Hz), 2.34 d.d (1H, 4-H$_{ax}$, $^3J_{4\text{-}ax,5\text{-}ax}$ = 11.9, $^3J_{4\text{-}ax,5\text{-}eq}$ = 4.6 Hz), 2.64–2.73 m (5H, 2-H$_{eq}$, 2′-H, 5′-H), 2.81 br.s (1H, 3-OH), 2.91 m (1H, 6-H$_{eq}$, $^2J_{6\text{-}eq,6\text{-}ax}$ = 11.3 Hz), 3.43 d (1H, PhC**H**$_2$, ^2J = 13.1 Hz), 3.54 d (1H, PhCH$_2$, ^2J = 13.1 Hz), 7.19–7.34 m (5H, Ph). ^{13}C NMR spectrum, δ$_C$, ppm: 22.38 (C^5); 23.56 (C$^{3'}$, C$^{4'}$); 24.40 (CH$_3$); 51.85 (C$^{2'}$, C$^{5'}$); 53.63, 62.50, 65.42, 68.26, 66.94 (C^2, C^4, C^6, Ph**C**H$_2$); 71.76 (C^3); 126.86, 128.12 (2C), 128.71 (2C), 138.73 (C$_{arom}$).

***trans*-1-Benzyl-3-methyl-4-phenylaminopiperidin-3-ol dihydrochloride (XIX)** was synthesized from 0.500 g (2.46 mmol) of compound **V** and 0.230 g (2.46 mmol) of aniline (reaction time 7 days). Yield 0.680 g (75%), colorless crystals, mp 224–225°C (from EtOH). Found, %: C 61.92, 61.73; H 7.15, 7.34; N 7.73, 7.34. $C_{17}H_{26}Cl_2N_2O$. Calculated, %: C 61.79; H 7.10; N 7.58.

***trans*-1-Benzyl-3-methyl-4-phenylaminopiperidin-3-ol (**free base**).** ^{1}H NMR spectrum, δ, ppm: 1.25 s (3H, 3-CH$_3$), 1.54 m (1H, 5-H), 2.02 m (1H, 5-H), 2.25–2.56 m (4H, 2-H, 6-H), 3.09 br.s (2H, NH, OH), 3.36 d.d (1H, 4-H, ^3J = 6.3, 4.5 Hz), 3.51 d (1H, PhC**H**$_2$, ^2J = 13.2 Hz), 3.56 d (1H, PhC**H**$_2$, ^2J = 13.2 Hz), 6.63–6.73 m (3H, NH**Ph**), 7.15 m (2H, NH**Ph**), 7.21–7.35 m (5H, CH$_2$**Ph**).

***trans*-1-Benzyl-3-hydroxypiperidine-4-carbonitrile hydrochloride (XX)** was synthesized from 0.19 g (1 mmol) of compound **IV** and 0.100 g (1.5 mmol) of KCN (reaction time 7 days). Yield 51%, colorless crystals, mp 164–165°C (decomp., from EtOH). Found, %: C 61.95; H 6.79; N 11.10. $C_{13}H_{17}ClN_2O$. Calculated, %: C 61.78; H 6.78; N 11.08.

***trans*-1-Benzyl-3-hydroxypiperidine-4-carbonitrile (**free base**).** R_f 0.4 (Silufol; hexane–acetone, 2:1). ^{1}H NMR spectrum, δ, ppm: 1.82 m (1H, 5-H, ^2J = 14.1, ^3J = 3.8, 7.03, 10.84 Hz), 2.09 m (1H, 5-H, ^2J = 13.48, ^3J = 3.98, 4.4, 8.21 Hz), 2.34–2.45 m (2H, 2-H$_{ax}$, 6-H$_{ax}$), 2.54–2.68 m (2H, 4-H$_{ax}$, 6-H$_{eq}$), 2.81 d.d (1H, 2-H$_{eq}$, $^2J_{2\text{-}eq,2\text{-}ax}$ = 11.6, $^3J_{2\text{-}eq,3\text{-}ax}$ = 2.9 Hz), 2.92 br.s (1H, 3-OH), 3.53 s (2H, PhC**H**$_2$), 3.92 t.d (1H, 3-H$_{ax}$, $^3J_{3\text{-}ax,2\text{-}ax}$ = 2.9, ^3J = 6.15, 6.95 Hz), 7.24–7.39 m (5H, Ph). ^{13}C NMR spectrum, δ$_C$, ppm: 25.56 (C^5); 33.55, 50.38, 57.28, 62.36 (C^2, C^4, C^6, Ph**C**H$_2$); 66.84 (C^3); 120.24 (CN); 127.39, 128.37 (2C), 128.94 (2C), 137.27 (C$_{arom}$).

***trans*-4-Azido-1-benzylpiperidin-3-ol hydrochloride (XXI)** was synthesized from 0.190 g (1.0 mmol) of compound **IV** and 0.065 g (1.5 mmol) of sodium azide (reaction time 7 days). Yield 56%, colorless crystals, mp 155–156°C (decomp., from EtOH).

***trans*-4-Azido-1-benzylpiperidin-3-ol (**free base**).** R_f 0.5 (Silufol; hexane–acetone, 2:1). ^{1}H NMR spectrum, δ, ppm: 1.65 m (1H, 5-H$_{ax}$, $^2J_{5\text{-}ax,5\text{-}eq}$ = 13.8, $^3J_{5\text{-}ax,6\text{-}eq}$ = 3.81, $^3J_{5\text{-}ax,4\text{-}ax}$ = 9.37, $^3J_{5\text{-}ax,6\text{-}ax}$ = 9.38 Hz), 1.99 m (1H, 5-H$_{eq}$, $^2J_{5\text{-}eq,5\text{-}ax}$ = 13.8 Hz), 2.10–2.23 m (2H, 2-H$_{ax}$, 6-H$_{ax}$), 2.63–2.73 m (2H, 3-OH, 6-H$_{eq}$), 2.87 d.d (1H, 2-H$_{eq}$, $^2J_{2\text{-}eq,2\text{-}ax}$ = 11.0, $^3J_{2\text{-}eq,3\text{-}ax}$ = 2.4 Hz), 3.31 m (1H, 4-H$_{ax}$, $^3J_{4\text{-}ax,5\text{-}eq}$ = 4.5, $^3J_{4\text{-}ax,3\text{-}ax}$ = 7.9, $^3J_{4\text{-}ax,5\text{-}ax}$ = 9.37 Hz), 3.51 (2H, PhC**H**$_2$, *AB* system,

^2J = 13.2 Hz), 3.60 t.d (1H, 3-H$_{ax}$, $^3J_{3\text{-}ax,2\text{-}eq}$ = 2.4, $^3J_{3\text{-}ax,4\text{-}ax}$ = 7.9 Hz), 7.23–7.34 m (5H, Ph). ^{13}C NMR spectrum, δ_C, ppm: 27.92 (C^5); 50.54, 57.19, 62.32, 63.54 (C^2, C^4, C^6, Ph**C**H$_2$); 69.85 (C^3), 127.26, 128.30 (2C), 128.98 (2C), 137.66 (C$_{arom}$).

***trans*-1-Benzyl-4-phenylsulfanylpiperidin-3-ol hydrochloride (XXII)** was synthesized from 0.190 g (1.0 mmol) of compound **IV** and 0.110 g (1.0 mmol) of benzenethiol (reaction time 6 h). Yield 69%, colorless crystals, mp 169–170°C (decomp., from EtOH). Found, %: C 64.16; H 6.48; N 3.99. $C_{18}H_{22}ClNOS$. Calculated, %: C 64.36; H 6.60; N 4.17.

***trans*-1-Benzyl-4-phenylsulfanylpiperidin-3-ol (**free base**).** R_f 0.6 (Silufol; hexane–acetone, 2:1). ^{1}H NMR spectrum, δ, ppm: 1.67 m (1H, 5-H$_{ax}$, $^2J_{5\text{-}ax,5\text{-}eq}$ = 13.48, $^3J_{5\text{-}ax,6\text{-}eq}$ = 3.81, $^3J_{5\text{-}ax,4\text{-}ax}$ = 9.1, $^3J_{5\text{-}ax,6\text{-}ax}$ = 9.4 Hz), 2.08 m (1H, 5-H$_{eq}$, $^2J_{5\text{-}eq,5\text{-}ax}$ = 13.48 Hz), 2.13–2.22 m (2H, 2-H$_{ax}$, 6-H$_{ax}$), 2.68 m (1H, 6-H$_{eq}$, $^2J_{6\text{-}eq,6\text{-}ax}$ = 11.5, $^3J_{6\text{-}eq,5\text{-}ax}$ = 3.81, $^3J_{6\text{-}eq,5\text{-}eq}$ = 5.2 Hz) 2.93 t.d (1H, 4-H$_{ax}$, $^3J_{4\text{-}ax,5\text{-}eq}$ = 4.6, $^3J_{4\text{-}ax,3\text{-}ax}$ = 7.68, $^3J_{4\text{-}ax,5\text{-}ax}$ = 9.1 Hz), 3.05 d.d.d (1H, 2-H$_{eq}$, $^2J_{2\text{-}eq,2\text{-}ax}$ = 11.0, $^3J_{2\text{-}eq,3\text{-}ax}$ = 3.3, $^4J_{2\text{-}eq,6\text{-}eq}$ = 1.1 Hz), 3.50 (2H, PhC**H**$_2$, *AB* system, ^2J = 13.48 Hz), 3.58 t.d (1H, 3-H$_{ax}$, $^3J_{3\text{-}ax,2\text{-}eq}$ = 3.3, $^3J_{3\text{-}ax,4\text{-}ax}$ = 7.68, $^3J_{3\text{-}ax,6\text{-}ax}$ = 8.1 Hz), 7.20–7.46 m (10H, H$_{arom}$).

Kinetic separation of a mixture of *cis*- and *trans*-1-benzyl-6-benzyloxymethyl-3,4-epoxypiperidines XXIIIa and XXIIIb (Table 2, run no. 1**).** A solution of 0.160 g (2.2 mmol) of diisopropylamine in 5 ml of anhydrous tetrahydrofuran was cooled to –10°C, 1.40 ml (2.2 mmol) of a 1.6 M solution of butyllithium in hexane was added under argon, the mixture was stirred for 30 min and cooled to –70°C, a solution of 0.310 g (1.0 mmol) of an equimolar mixture of stereoisomers **XXIIIa** and **XXIIIb** in 3 ml of anhydrous THF was added, and the mixture was left to stand for 2.5 h at 10°C. It was then treated with 10 ml of a saturated aqueous solution of ammonium chloride and extracted with methylene chloride (5×10 ml). The extracts were combined and dried over sodium sulfate, the solvent was removed under reduced pressure, and the residue was applied to a column charged with silica gel in hexane. The column was eluted with hexane–ethyl acetate (gradient elution, 0 to 20% of EtOAc), and chromatographically similar fractions were combined.

***cis*-1-Benzyl-6-benzyloxymethyl-1,2,3,6-tetrahydropyridin-3-ol (XXVIa).** Yield 0.045 g (15%), light yellow oily substance, R_f 0.5 (Silufol, hexane–acetone, 5:1). ^{1}H NMR spectrum, δ, ppm: 2.28 br.s (1H, 3-OH), 2.46 d.d (1H, 2-H, ^2J = 11.9, $^3J_{2,3}$ = 2.3 Hz), 2.86 d.d (1H, 2-H, ^2J = 11.9, $^3J_{2,3}$ = 2.8 Hz), 3.20 m (1H, 6-H), 3.43 d (1H, PhC**H**$_2$N, ^2J = 13.6 Hz), 3.53 d.d (1H, 6-CH$_2$, ^2J = 9.6, ^3J = 5.6 Hz), 3.73 d.d (1H, 6-CH$_2$, ^2J = 9.6, ^3J = 4.3 Hz), 3.93 m (1H, 3-H), 4.12 d (1H, PhC**H**$_2$N, ^2J = 13.6 Hz), 4.53 s (2H, PhC**H**$_2$O), 5.85 d.d (1H, =CH, $^3J_{5,4}$ = 9.9, ^3J = 2.3 Hz), 6.01 d.d.d (1H, =CH, $^3J_{4,5}$ = 9.9, ^3J = 4.9, J = 2.3 Hz), 7.20–7.37 m (10H, Ph).

***trans*-1-Benzyl-6-benzyloxymethyl-1,2,3,6-tetrahydropyridin-3-ol (XXVIb).** Yield 0.065 g (21%), light yellow oily substance, R_f 0.5 (Silufol, hexane–acetone, 5:1). ^{1}H NMR spectrum, δ, ppm: 2.00 br.s (1H, 3-OH), 2.32 d.d (1H, 2-H, ^2J = 11.5, $^3J_{2,3}$ = 5.8 Hz), 3.04 d.d (1H, 2-H, ^2J = 11.5, $^3J_{2,3}$ = 4.3 Hz), 3.32 m (1H, 6-H), 3.49 d.d (1H, 6-CH$_2$, ^2J = 9.9, ^3J = 5.6 Hz), 3.64 d (1H, PhC**H**$_2$N, ^2J = 13.8 Hz), 3.69 d.d (1H, 6-CH$_2$, ^2J = 9.9, ^3J = 4.8 Hz), 3.95 d (1H, PhC**H**$_2$N, ^2J = 13.8 Hz), 4.07 m (1H, 3-H), 4.52 s (2H, PhC**H**$_2$O), 5.83 d.d.d (1H, =CH, $^3J_{5,4}$ = 10.1, ^3J = 2.8, ^4J = 0.8 Hz), 5.89 d.d.d (1H, =CH, $^3J_{4,5}$ = 10.1, ^3J = 2.8, ^4J = 2.0 Hz), 7.21–7.36 m (10H, Ph). **XXVIa**/**XXVIb** picrate, mp 157–158°C (from EtOH). Found, %: C 58.23; H 4.65; N 10.31. $C_{26}H_{26}N_4O_9$. Calculated, %: C 57.99; H 4.87; N 10.40.

Recovery of initial compound **XXIIIa** 0.090 g (30%). ^{1}H NMR spectrum, δ, ppm: 2.00–2.11 m (2H, 5-H, $^2J_{5\text{-}ax,5\text{-}eq}$ = 15.3, $^3J_{5\text{-}ax,6}$ = 5.8, $^3J_{5\text{-}eq,6}$ = 5.8, $^3J_{5\text{-}ax,4}$ = 1.3, $^3J_{5\text{-}eq,4}$ = 3.0 Hz), 2.83 d.d (1H, 2-H$_{ax}$, $^2J_{2\text{-}ax,2\text{-}eq}$ = 14.4, $^3J_{2\text{-}ax,3}$ = 3.8 Hz), 2.92 m (1H, 6-H), 3.02 d (1H, 2-H$_{eq}$, $^2J_{2\text{-}eq,2\text{-}ax}$ = 14.4 Hz), 3.12 t (1H, 3-H, $^3J_{3,4}$ = 3.5, $^3J_{3,2\text{-}ax}$ = 3.8 Hz), 3.24 m (1H, 4-H), 3.43 d.d (1H, 6-CH$_2$, ^2J = 9.7, ^3J = 5.3 Hz), 3.69 d (1H, PhC**H**$_2$N, ^2J = 13.4 Hz), 3.76 d (1H, PhC**H**$_2$N, ^2J = 13.4 Hz), 3.78 d.d (1H, 6-CH$_2$, ^2J = 9.7, ^3J = 6.6 Hz), 4.47 s (2H, PhC**H**$_2$O), 7.20–7.36 m (10H, Ph).

(3*SR*,4*SR*,6*RS*)-1-Benzyl-4-benzylamino-6-benzyloxymethylpiperidin-3-ol dihydrochloride (XXIV) was synthesized from 0.100 g (0.32 mmol) of compound **XXIIIa** and 0.030 g (0.32 mmol) of benzylamine (reaction time 24 h). Yield 0.115 g (88%), colorless crystals, mp 235–236°C (from EtOH). Found, %: C 66.44; H 7.10; N 5.80. $C_{27}H_{34}Cl_2N_2O_2$. Calculated, %: C 66.25; H 7.00; N 5.72.

(3*SR*,4*SR*,6*RS*)-1-Benzyl-4-benzylamino-6-benzyloxymethylpiperidin-3-ol (free base**).** ^{1}H NMR spectrum, δ, ppm: 1.42 m (1H, 5-H$_{ax}$, $^2J_{5\text{-}ax,5\text{-}eq}$ = 13.9, $^3J_{5\text{-}ax,6\text{-}eq}$ = 5.5, $^3J_{5\text{-}ax,4\text{-}ax}$ = 9.6 Hz), 1.86 br.s (2H, NH, OH), 2.12 m (1H, 5-H$_{eq}$), 2.39 d.d (1H, 2-H$_{ax}$, $^2J_{2\text{-}ax,2\text{-}eq}$ = 11.6, $^3J_{2\text{-}ax,3\text{-}ax}$ = 8.6 Hz), 2.54 d.d.d (1H, 4-H$_{ax}$, $^3J_{4\text{-}ax,5\text{-}ax}$ = 9.6, $^3J_{4\text{-}ax,3\text{-}ax}$ = 8.1, $^3J_{4\text{-}ax,5\text{-}eq}$ = 4.0 Hz),

2.68 d.d (1H, 2-H_{eq}, $^2J_{2\text{-}eq,2\text{-}ax}$ = 11.9, $^3J_{2\text{-}eq,3\text{-}ax}$ = 4.3 Hz), 3.03 m (1H, 6-H_{eq}), 3.35 t.d (1H, 3-H_{ax}, $^3J_{3\text{-}ax,2\text{-}ax}$ = 8.6, $^3J_{3\text{-}ax,4\text{-}ax}$ = 8.1, $^3J_{3\text{-}ax,2\text{-}eq}$ = 4.3 Hz), 3.44 d (1H, PhC**H**$_2$N, ^2J = 13.5 Hz), 3.50 d (1H, PhC**H**$_2$N, ^2J = 13.2 Hz), 3.55 d (1H, PhC**H**$_2$N, ^2J = 13.2 Hz), 3.58–3.63 m (2H, 6-CH_2), 3.80 d (1H, PhC**H**$_2$N, ^2J = 13.5 Hz), 4.49 s (2H, PhC**H**$_2$O), 7.20–7.35 m (10H, Ph).

This study was performed under financial support by the Russian Foundation for Basic Research (project nos. 08-03-00266a, 05-03-32658a).

REFERENCES

1. Lohse, A., Jensen, H., Bach, P., and Bols, M., *J. Chem. Soc., Perkin Trans. 1*, 2000, p. 659.
2. Bernotas, R.C. and Ganem, B., *Carbohydr. Res*., 1987, vol. 167, p. 312.
3. Buchheit, K., Gamses, R., Giger, R., Hoyer, D., Klein, F., Kloppner, E., Pfannkuche, H., and Mattes, H., *J. Med. Chem*., 1995, vol. 38, p. 2326.
4. Monkovic, I., Brown, M., Luke, G.M., Standridge, R.T., Willner, D., Crosswell, A.R., Algieri, A., Buyniski, J.P., Crenshaw, R.R., and Juby, P.F., *Eur. J. Med. Chem*., 1989, vol. 24, p. 233.
5. Ishibashi, M., Ohizumi, Y., Sasaki, T., Nakamura, H., Hirata, Y., and Kobayashi, J., *J. Org. Chem*., 1987, vol. 52, p. 450.
6. Kiguchi, T., Yuumoto, Y., Ninomiya, I., Naito, T., Deki, K., Ishibashi, M., and Kobayashi, J., *Tetrahedron Lett*., 1992, vol. 33, p. 7389.
7. Kobayashi, J., Naitoh, K., Doi, Y., Deki, K., and Ishibashi, M., *J. Org. Chem*., 1995, vol. 60, p. 6941.
8. Freyer, A.J., Patil, A.D., Killmer, L., Troupe, N., Mentzer, M., Carte, B., Faucette, L., and Johnson, R.K., *J. Nat. Prod*., 1997, vol. 60, p. 986.
9. Cossy, J., Molina, J.L., and Desmurs, J., *Tetrahedron Lett*., 2001, vol. 42, p. 5713.
10. Langlois, N. and Calvez, O., *Synth. Commun*., 1998, vol. 28, p. 4471.
11. Clinch, K., Vasella, A., and Schauer, R., *Tetrahedron Lett*., 1987, vol. 21, p. 6425.
12. Parr, B. and Horestein, B.A., *J. Org. Chem*., 1997, vol. 62, p. 7489.
13. Brimacombe, J.S. and Mofti, A.M., *Carbohydr. Res*., 1971, vol. 16, p. 167.
14. Grishina, G.V., Borisenko, A.A., Veselov, I.S., and Petrenko, A.M., *Russ. J. Org. Chem*., 2005, vol. 41, p. 272.
15. Boto, A., Hernandez, R., de Leon, Y., Murguia, J.R., and Rodriguez-Afonso, A., *Eur. J. Org. Chem*., 2005, p. 673.
16. Zhao, S., Ghosh, A., D'Andrea, S.V., Freeman, J.P., Von Voigtlander, P.F., Carter, D.B., Smith, M.W., Blinn, J.R., and Szmuszkovicz, J., *Heterocycles*, 1994, vol. 39, p. 163.
17. Efange, S.M.N., Khare, A.B., Akell, F.S.K., and Parsons, S.M., *J. Med. Chem*., 1997, vol. 40, p. 3905.
18. Efange, S.M.N., Khare, A., Parsons, S.M., Bau, R., and Metzenthin, T., *J. Med. Chem*., 1993, vol. 36, p. 985.
19. Ganina, O.G., Veselov, I.S., Fedorov, A.Yu., Grishina, G.V., and Beletskaya, I.P., *Izv. Ross. Akad. Nauk, Ser. Khim*., 2006, p. 1583.