Optically pure *trans*-1-benzyl-4-aminopiperidin-3-ols. Synthesis and absolute configuration

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DOI: http://dx.doi.org/10.3998/ark.5550190.0012.a09

Abstract

Enantiomerically pure *trans*-(*3R,4R*)-4-aminopiperidin-3-ols, which are convenient precursors for making natural and synthetic aminohydroxylated piperidine alkaloid analogs, were efficiently synthesized through the reaction of enantiomerically pure (*3R,4S*)-3,4-epoxypiperidine with amines in the presence of $LiClO_4$ in CH_3CN at room temperature. The absolute stereochemistry of the resultant amino alcohols was determined by the stereochemical correlation method and single-crystal X-ray analysis.

Keywords: β-Aminoalcohol, piperidine, epoxide, optical activity, absolute stereochemistry

Introduction

Numerous amino- and hydroxysubstituted piperidine derivatives constitute a subclass of hydroxylated piperidine alkaloids, also referred to as iminosugars, and are known as potent inhibitors of glycosidases and related enzymes.

Pseudodistomins **A-F**, novel potent antineoplastic aminohydroxylated piperidine alkaloids with calmodulin antagonistic and antitumor activities, have recently become of great interest (Figure 1).[1,2]

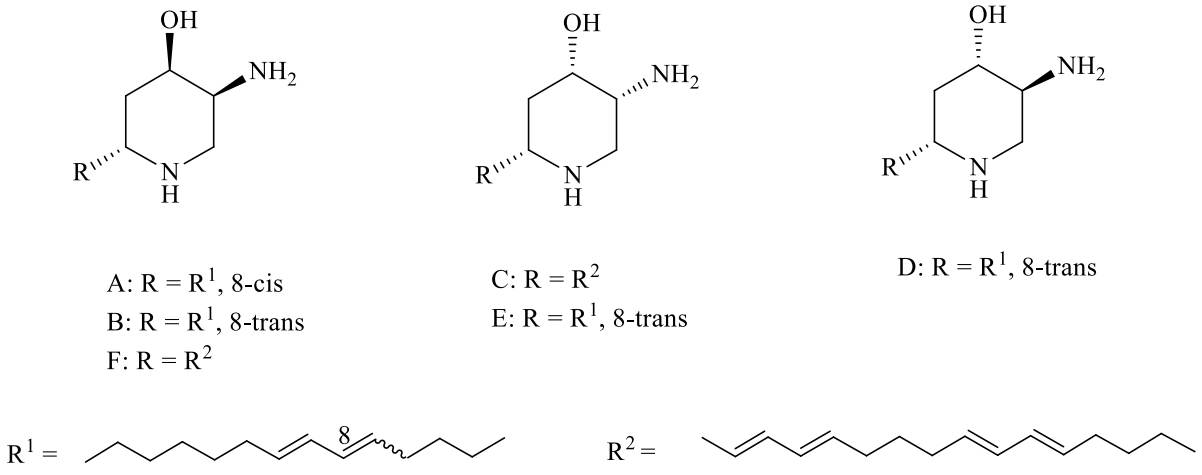


Figure 1

The presence of an amino group in the iminosugar structure leads to selective inhibition of some kinds of glycosidases and hexoaminidases. For example, aminodihydroxypiperidine **2**, which is an amino analog of isofagomine **1**, exhibits selective inhibition activity toward β-glucosidase.[3] The acetylamino derivative of 1-deoxynojirimycin **3** is a selective inhibitor of β-N-acetylaminoglucosaminidase.[4] Cisapride, a potent gastric prokinetic agent with reduced dopamine D_2 receptor antagonist activity,[5] is a *cis*-4-amino-3-hydroxypiperidine derivative (Fig. 2).

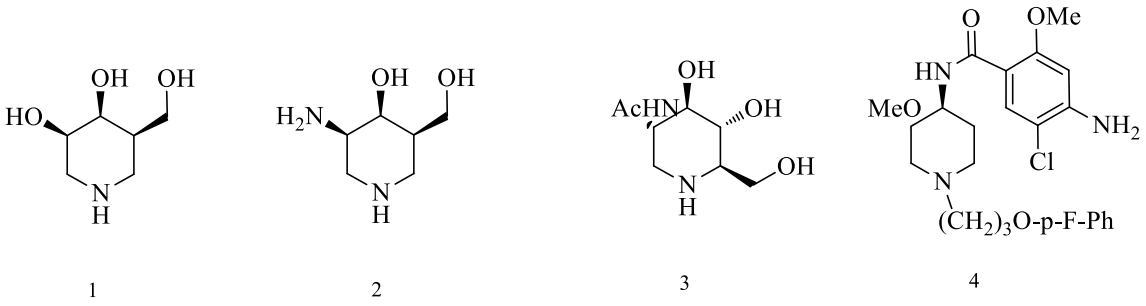


Figure 2

Nowadays aminohydroxylated piperidine alkaloids and their synthetic analogs have drawn significant attention owing to their ability to mimic sugars and selectively inhibit glycosidases and glycoprotein-processing enzymes.[6,7]

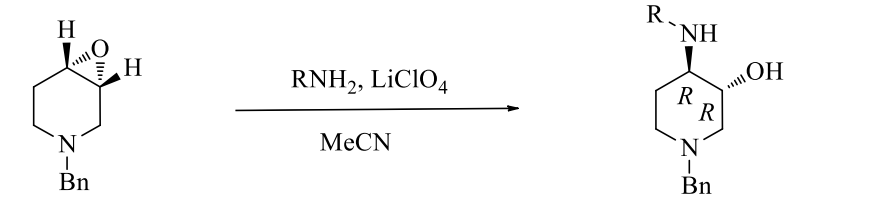
The high therapeutic potential of these inhibitors for treatment of a variety of carbohydrate-mediated diseases – such as diabetes, cancer, and viral infections including HIV – has evoked considerable efforts aimed at their structural modifications and synthesis of their analogs.

Results and Discussion

Herein we describe a concise synthesis of enantiomerically pure *trans*-4-aminopiperidin-3-ols **(–)-5-(–)-7**, which are closely related to natural aminohydroxylated piperidine alkaloids. In view of the known dependence between the biological activity of a molecule and its absolute configuration, the synthesis of enantiopure aminohydroxylated piperidine derivatives is highly promising from both synthetic and pharmacological standpoints.[4,8-10]

Previously we have developed a methodology for scalable regio- and stereospecific synthesis of (±)-*trans*-4-aminopiperidin-3-ols based on the interaction of 1-benzyl-3,4-epoxypiperidines with C-, N- and S-nucleophiles in the presence of lithium perchlorate.[11] This methodology has opened an opportunity for obtaining optically active piperidine amino alcohols and using them as new chiral ligands in asymmetric synthesis and asymmetric catalysis, as well as in search of new antiviral prodrugs.

Now we report on the synthesis of some enantiomerically pure *trans*-(*3R,4R*)-4-aminopiperidin-3-ols (*3R,4R)*-**5-7** through interaction of optically pure (*3R,4S*)-(–)-3,4-epoxypiperidine (*3R,4S*)-**4** with various amines, such as benzylamine**,** (*S*)-1-phenylethylamine and 2-hydroxyethylamine, in the presence of $LiClO_4$ in CH_3CN at room temperature, according to our method reported earlier[11] (Scheme 1).



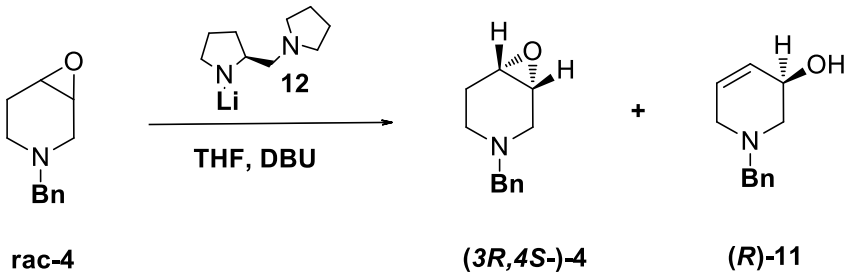
(-)-(*3R,4S*)-**4**

(-)-(*3R,4R*)-**5** R=Bn
(-)-(*3R,4R*)-**6** R=CH(Me)Ph
(-)-(*3R,4R*)-**7** R=CH_2CH_2OH

Scheme 1. Conditions: rt, 24h, 75-85%.

After standard treatment of reaction mixtures, individual amino alcohols (–)-**5** to (–)-**7** were isolated in the form of dihydrochlorides or dihydrobromides. Their chemical individuality was confirmed by elemental analysis. ^1H and ^{13}C NMR spectra confirmed formation of only one diastereomer of amino alcohols (–)-**5** to (–)-**7** in each reaction.

The initial (*3R,4S*)-epoxide (*3R,4S*)-**4** with 98.7% *ee* was obtained by kinetic resolution of (±)-1-benzyl-3,4-epoxypiperidine (*rac*-**4**)[12] **(**1 mmol**)** under treatment with lithium amide **12** (0.95 mmol), which was prepared from (+)-(*S*)-2-(pyrrolidin-1-yl)methylpyrrolidine [13], and DBU (0.95 mmol) (Scheme 2).[14]



Scheme 2. Conditions: – 70 ºC – rt, 12h.

Individual epoxide (*3R,4S*)-**4** with 98.7% *ee* and allylic alcohol (*R*)-**11** (18.3% *ee*) were isolated in ratio 1:5 and 87% overall yield by column chromatography on silica gel.

The optical purity of (*3R,4S*)-epoxide (–)-**4** was confirmed by comparison of the specific rotation values for (*3R,4S*)-**4** and enantiomerically pure (*3R,4S*)-epoxide (–)-**4** obtained earlier.[14]

The stereochemistry of the target amino alcohols (–)-**5** to (–)-**7** was determined on the basis of ^{1}H and ^{13}C NMR spectral data, as well as by comparison with the corresponding *rac*-**5,6**.[11] The large values of vicinal coupling constants $^{3}J_{3a,4a}$ of the axial protons connected to the C-3 and C-4 stereocenters of the piperidine core indicated that amino alcohols (–)-**5** to (–)-**7** are *trans*-isomers. The data provided here prove that the 3-hydroxy and 4-amino groups have equatorial orientations (Table 1).

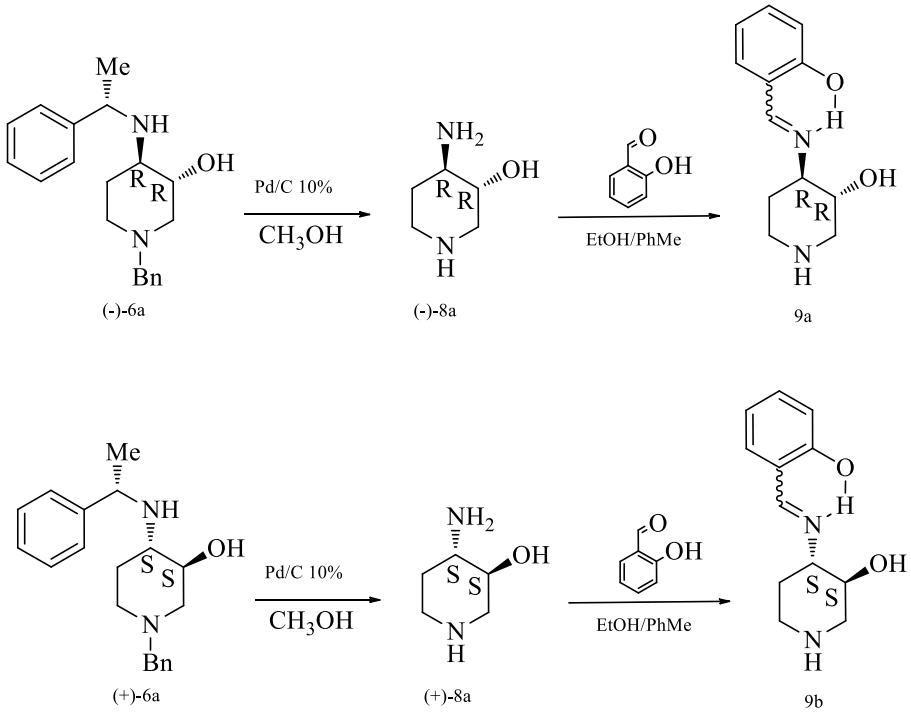
Table 1. Selected coupling constants for amino alcohols **5**, **6 (6a)**, **6b**, **7**, **8**

Compound	**5**	**6 (or 6a)**	**6b**	**7**	**8**
$^{3}J_{2e,3a}$	4.4	4.4	4.1	4.4	4.8
$^{3}J_{2a,3a}$	9.7	9.7	8.9	9.5	11.1
$^{4}J_{2e,6e}$	1.8	1.6	1.5	1.0	1.0
$^{3}J_{3a,4a}$	**9.1**	**9.5**	**9.3**	**9.9**	**10.4**
$^{3}J_{5e,4a}$	4.1	-	3.9	4.0	3.8
$^{3}J_{5a,4a}$	10.9	11.2	10.9	12.1	12.6
$^{3}J_{5a,6e}$	4.5	4.0	4.0	3.7	4.3
$^{3}J_{5a,6a}$	12.9	11.6	11.4	11.9	13.3
$^{3}J_{5e,6e}$	-	-	3.4	-	-
$^{3}J_{5e,6a}$	-	1.8	3.4	2.4	3.0

The absolute stereochemistry of the target amino alcohols **5-7** was established by the *N*-salicylidenimine chirality rule, which correlates the absolute configuration of the *N*-salicylidene derivative of a chiral alkylamine with its circular dichroism spectra.[15,16]

N-Salicylidenimine derivatives **9a, 9b** of amines **8a, 8b** were synthesized starting from diastereomers (–)-**6a** and (+)-**6b** (Scheme 3)**.** For this purpose, diastereomers (–)-**6a** and (+)-**6b**

were synthesized by interaction of *rac*-epoxide, *rac*-**4** with **(**–**)-(**1*S*)-phenylethylamine in the presence of lithium perchlorate.



Scheme 3

The ^{1}H NMR spectrum study of the reaction mixture showed the formation of diastereomeric pair **6a,b** in the 1:1 ratio. Individual diastereomers (–)-**6a** and (+)-**6b** were isolated by column chromatography over silica gel (the eluent was hexane : ethyl acetate : methanol 3:1:0.1) with 86% overall yield and 99% *de* (Table 2).

Comparing the signs and values of specific rotation and also the ^{1}H NMR spectra of isomers (–)-**6** and **(–)-6a,** (+)-**6b**, we have found that **(–)-6** and (–)-**6a** have identical ^{1}H NMR data, as well as specific rotation values. This means that aminoalcohol (–)-**6** also has 99 % *ee*.

Table 2. Characteristic properties of amino alcohols **5-8,11**

Compound	$[\alpha]_D^{20}$	*ee* (%)	*de* (%)	yield (%)
(–)-**5**	–58.5 (c 0.20, $CHCl_3$)	99		85
(–)-**5′** [17]	–62.5 (c 3.42)[c]			
(–)-**6**	–71.8 (c 0.30, $CHCl_3$)	99		87
(–)-**6a**[a]	–71.8 (c 0.30, $CHCl_3$)		99	41
(+)-**6b**[a]	+13.3 (c 0.20, $CHCl_3$)		99	45
(–)-**7**	–19.3 (c 0.10, H_2O)[b]	99		

(–)-**8a**	–19.2 (c 0.05, H_2O)[b]			87

Table 2. Continued

Compound	[α]D20	**ee (%)**	**de (%)**	yield (%)
(+)-**8b**	+18.9 (c 0.07, H_2O)[b]			85
(–)-**11**	–16.2 (c 0.20, $CHCl_3$)	18.3		72.5

[a]Obtained from *rac*-**4**. [b]As dihydrochloride. [c]Solvent was indicated.

Further, *trans*-4-amino-3-hydroxypiperidine enantiomers (–)-**8a** and (+)-**8b** were obtained by removing the 1-benzyl and 1-(*S*)-phenylethyl groups from diastereomers (–)-**6a** and (+)-**6b**, respectively, through hydrogenolysis above Pd/C. The *N*-salicylidenimine derivatives **9a** and **9b** were obtained by condensation of enantiomers (–)-**8a** and (+)-**8b**, respectively, with salicylic aldehyde (Scheme 3).

For *N*-salicylidene derivatives of chiral alkylamines, the planar sector rule predicts that the negative sign of the Cotton effects near 315 and 250 nm corresponds to negative chirality ((R) configuration).

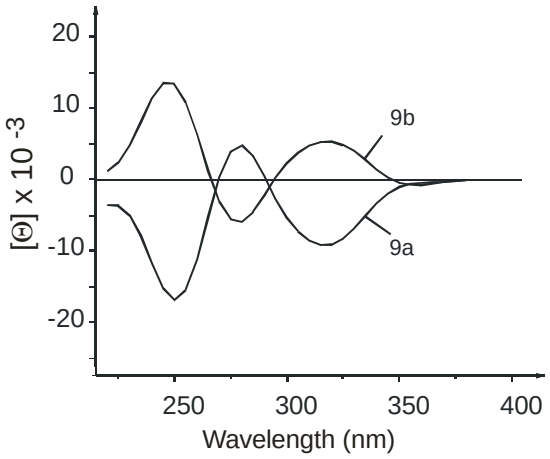


Figure 3. CD curves of diastereomers **9a** and **9b** in $CHCl_3$.

We have analyzed the circular dichroism (CD) data of both derivatives **9a** and **9b** in $CHCl_3$ (room temperature). As it is shown in Figure 3, three Cotton effects in the CD curve of derivative **9a** – negative at 322 and 250 nm and positive at 276 nm – are attributed to transitions of the salicylidenimino chromophore with an intramolecular hydrogen bond.[16] For the *N*-salicylidenimino derivative **9a**, the observable negative Cotton effects at 322 and 250 nm correspond to the negative sign of chirality; thus, derivative **9a** has the (*3R*,*4R*) configuration.

The CD spectrum **9b** in $CDCl_3$ exhibits an almost mirror image of the **9a** spectrum: there are less intense positive Cotton effects at 322 and 250 nm (room temperature), which correspond to positive chirality (Fig. 3). Thus **9b** has to have the (*3S,4S*) configuration.

There is no change in the absolute stereochemistry of the 3- and 4-centers of the piperidine core during the synthesis of enantiomers **9a, 9b**; therefore, the absolute configuration of parent **(–)-6a** should also be (*3R,4R*).

To our knowledge, there has been only one report on the synthesis of optically active *trans*-(*3S,4S*)-**(–)**-1-benzyl-4-benzylaminopiperidin-3-ol ((*3S,4S*)-**5′**)[17], in which the (*3S,4S*) stereochemistry of aminoalcohol **5′** had been suggested on the basis of the stereochemical scheme of its synthesis from (*S*)-pyroglutaminol. In this connection we have tested validation of configuration determination.

Unambiguous confirmation of the (*3R,4R***)** stereochemistry of dihydrobromide (–)-**6** was determined by single-crystal X-ray analysis (Fig. 4), using the 4-(1′*S***)**-phenylethyl substituent as a chiral marker.

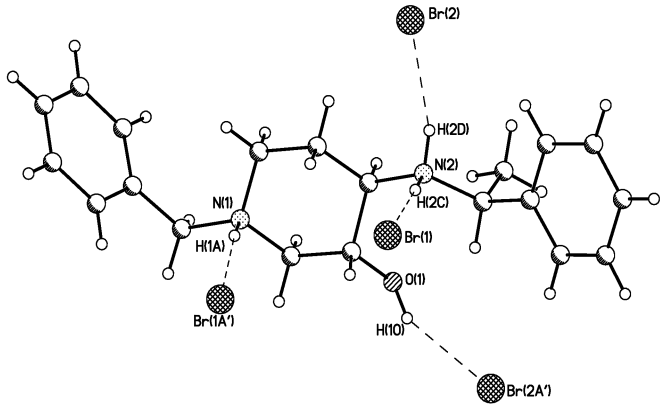


Figure 4. X-ray structure of dihydrobromide of (–)-**6**.

X-Ray data show the (*3R,4R*) configuration of 3- and 4-stereogenic centers in amino alcohol dihydrobromide (–)-**6.** Thus, determination of the absolute configuration of (–)-**6** by X-ray analysis and stereochemical correlation yielded identical results. Consequently, all amino alcohols **5-7,** which belong to the same stereochemical line, have the (*3R,4R*)-configuration. Furthermore, we compared the chiroptical properties of amino alcohol (*3R,4R*)-**5** and known (–)-**5**′.

Both amino alcohols, (–)-**5** and known (**–**)-**5′** have the same negative sign and similar values of specific rotation (Table 2); therefore, they should have the same (*3R,4R*) stereochemistry. These results make it possible to specify the (*3R,4R*) configuration of earlier described[17] (**–**)-1-benzyl-4-benzylaminopiperidin-3-ol, (–)-**5**′.

Conclusions

Our results showed that various optically pure *trans*-(*3R,4R*)-4-aminopiperidin-3-ols can be conveniently prepared through *trans* ring opening of optically pure (*3R,4S*)-epoxide **4** with various amines. We hope that our results may be useful in directed chiral synthesis of natural and synthetic aminohydroxylated piperidine alkaloid analogs with the required biological activities.

Experimental Section

The NMR spectra were recorded on Varian VXR-400 spectrometer using chloroform-*d* as solvent. Chemical shifts are given in δ (ppm) relative to TMS as internal standard. Elemental analysis was performed with a Perkin-Elmer 2400 CHNS elemental analyzer. Silica gel 60 was used for column chromatography. Merck Kieselgel 60 and Silufol were used for TLC. Optical rotations were measured on Perkin-Elmer 14. The CD spectra were registered on a Jasco-720 instrument using a 0.1 cm optical-path length cuvette.

(–)-(3*R*,4*S*)-1-Benzyl-3,4-epoxypiperidine, ((–)-**4**)**,** 98,7% *ee*, $[\alpha]_D^{20}$ –4.60 (*c* 0.20, $CHCl_3$) and allylic alcohol (–)-**11**, 14% ee, $[\alpha]_D^{20}$ –16.2 (*c* 0.20, $CHCl_3$) were obtained in 77 % overall yield according to described procedures.[14] Analytical data of (–)-**4** were consistent with those obtained for *rac*-**4**.[12]

General method for epoxide ring opening reactions. An appropriate amine (0.5 mmol) was added to stirred solution of (**–**)-(*3R,4S*)-epoxide (–)-**4** (0.5 mmol) and lithium perchlorate (0.5 mmol) in dry MeCN (5 mL). Reaction mixture was stirred for 24 h at room temperature, then water (3 mL) was added. MeCN was evaporated under reduced pressure, and residue was extracted with CH_2Cl_2 (5×2 mL), dried over Na_2SO_4 and filtered off. Solvent was evaporated at reduced pressure. The salts were formed by the addition of concentrated HCl (or HBr) to an ice cooled solution of the resulting viscous oil in absolute EtOH (10 mL) up to pH 4. Then the solvent was evaporated at reduced pressure and the remaining solid was dried over NaOH and P_2O_5 in vacuum desiccator. The solid was recrystallized from EtOH to give dihydrobromide of (–)-**6,** dihydrochlorides of the (–)-**5** and (–)-**7** as white crystals.

(–)-(3*R*,4*R*)-1-Benzyl-4-benzylaminopiperidin-3-ol, ((–)-**5**)**, dihydrochloride,** Yield 86%, white crystals, mp 213-214 °C. Anal. Calcd for $C_{19}H_{26}Cl_2N_2O$: C, 61.79; H, 7.10; N, 7.58. Found: C, 61.84; H, 7.25; N, 7.38. For free base: $[\alpha]_D^{20}$ –58.5 (*c* 0.2, $CHCl_3$). IR: (vaseline oil) ν 3300 cm^{-1} (NH). ^1H NMR (400 MHz, $CDCl_3$) δ 1.33 (m, 1H, H5$_a$), 1.90 (dd, *J* 10.5, 9.7 Hz, 1H, H2$_a$), 1.95-2.03 (m, 2H, H6$_a$, H5$_e$), 2.03 (ddd, *J* 10.9, 9.1, 4.1 Hz, 1H, H4$_a$), 2.60 (br s, 2H, OH, NH), 2.80 (br d, *J* 10.7 Hz, 1H, H6$_e$), 2.98 (ddd, *J* 10.5, 4.4, 1.8 Hz, 1H, H2$_e$), 3.43 (ddd, *J* 9.7,

9.1, 4.4 Hz, 1H, H3$_a$), 3.49 (AB-system, *J* 12.9 Hz 2H, Ph-CH_2), 3.65 (d, *J* 13.2 Hz, 1H, Ph-CH_2), 3.87 (d, *J* 13.2 Hz, 1H, Ph-CH_2) 7.21-7.32 (m, 10H, 2×Ph). ^{13}C NMR (100MHz, $CDCl_3$) δ 29.3, 50.7, 52.0, 58.5, 61.0, 62.5, 70.7, 127.0 (2C), 128.0 (2C), 128.1 (2C), 128.4 (2C),129.0 (2C), 138.0, 140.2.

(–)-(3*R*,4*R*)-1-Benzyl-4-[(1'*S*)-phenylethylamino]piperidin-3-ol, ((–)-**6**)**, dihydrobromide** Yield 84%, white crystals . The crystals suitable for X-ray analysis were grown up from EtOH. For free base: $[\alpha]_D^{20}$ –71.1 (*c* 0.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (dddd, *J* 12.4, 11.6, 11.2, 4.0 Hz, 1H, H5$_a$), 1.35 (d, *J* 6.6 Hz, 3H, CH_3), 1.78 (dd, *J* 10.4, 9.7 Hz, 1H, H2$_a$), 1.87 (ddd, *J* 11.7, 11.6, 1.8 Hz, 1H, H6$_a$), 1.97-2.10 (m, 2H, H5$_e$, H4$_a$), 2.69 (br s, 2H, OH, NH), 2.77 (br d, *J* 11.7 Hz, 1H, H6$_e$,), 2.99 (ddd, *J* 10.4, 4.4, 1.6 Hz, 1H, H2$_e$,), 3.40 (ddd, *J* 9.7, 9.5, 4.4 Hz, 1H, H3$_a$), 3.47 (AB-system, *J* 13.1 Hz 2H, Ph-CH_2), 3.96 (q, J 6.6 Hz, 1H, CHCH_3), 7.19-7.34 (m, 10H, 2×*Ph*). ^{13}C NMR (100MHz, $CDCl_3$) δ 25.2, 29.0, 51.9, 54.2, 58.2, 58.4, 62.4, 70.9, 126.5 (2C), 127.0, 127.1, 128.1 (2C), 128.6 (2C), 129.0 (2C), 137.8, 144.4.

Mixture of diastereomers (–)-**6a** and (+)-**6b** was obtained in 1:1 ratio according to ^{1}H NMR spectrum by interaction of epoxide *rac*-**4** with (–)-(1S)-phenylethylamine, $[\alpha]_D^{20}$ –39.5 (neat). Dihydrochlorides, white crystals are prepared as usually. Anal. Calcd $C_{20}H_{28}Cl_2N_2O$: C, 62.66; H, 7.36; N, 7.31. Found for (–)-**6a,** (+)-**6b**: C, 62.76; H, 7.35 N, 7.30.

The free bases (–)-**6a** and (+)-**6b** as individual isomers were separated by flash column chromatography over silica gel (eluent hexane : ethyl acetate : methanol, 3:1:0.1).

Yields 41% and 45%, respectively, transparent oils. (–)-(*3R,4R*)-**6a**: The ^{1}H NMR data and specific rotation values of amino alcohols (–)-**6** and (-)-**6a** were identical.

(+)-(*3S,4S*)-**6b**: $[\alpha]_D^{20}$ +13.3 (*c* 0.2, $CHCl_3$), ^{1}H NMR (400MHz, $CDCl_3$) δ 1.18 (dddd, *J* 12.9, 11.4, 10.9, 4.0 Hz, 1H, H5$_a$,), 1.32 (d, *J* 6.6 Hz, 3H, CH_3), 1.77 (m, 1H, H5$_e$), 1.93-2.02 (m, 2H, H2$_a$, H6$_a$), 2.10 (br s, 2H, OH, NH), 2.36 (ddd, *J* 10.9, 9.3, 3.9 Hz, 1H, H4$_a$), 2.72 (br d, *J* 11.6 Hz, 1H, H6$_e$), 3.07 (ddd, *J* 10.6, 4.1, 1.5 Hz, 1H, H2$_e$), 3.35 (ddd, *J* 9.3, 8.9, 4.1 Hz, 1H, H3$_a$,), 3.50 (AB-system, *J* 13.4 Hz 2H, Ph-CH_2), 3.89 (q, *J* 6.6 Hz, 1H, CHCH$_3$), 7.20-7.33 (m, 10H, 2×*Ph*). ^{13}C NMR (100MHz, $CDCl_3$) δ 23.7, 30.3, 52.3, 55.6, 58.3, 59.8, 62.6, 71.7, 126.4, 127.0 (2C), 128.2 (2C), 128.5 (2C), 129.1 (2C), 138.0, 146.6.

(–)-(3*R*,4*R*)-1-Benzyl-3-hydroxy-4-(2-hydroxyethylamino) piperidine ((–)-**7**)**, dihydrochloride,** yield 75%, white crystals, mp 144-145 ºC. Anal. Calcd for $C_{14}H_{24}Cl_2N_2O_2$: C, 52.02; H, 7.48; N, 8.67. Found: C, 51.80; H, 7.39; N, 8.45. $[\alpha]_D^{20}$ –19.3 (*c* 0.1, H_2O). For free base: ^{1}H NMR (400MHz, $CDCl_3$) δ 1.58 (qd, *J* 12.0, 3.7 Hz, 1H, H5$_a$), 1.80 (m, 1H, H5$_e$), 1.92 (dd, *J* 10.8, 9.5 Hz, 1H, H2$_a$), 2.01 (ddd, *J* 12.0, 11.7, 2.4 Hz, 1H, H6$_a$), 2.23 (ddd, *J* 12.0, 9.9, 4.0 Hz, 1H, H4$_a$), 2.60-2.90 (m, 5H, NH-CH_2, H6$_e$, NH, OH), 3.12 (ddd, *J* 10.8, 4.4, 1.0 Hz, 1H, H2$_e$), 3.47 (br s, 1H, OH), 3.47-3.55 (m, 4H, Ph-CH_2, HO-CH_2), 3.60 (ddd, *J* 9.9, 9.5, 4.4Hz, 1H, H3$_a$), 7.21-7.32 (m, 5H, Ph).

(–)-(3*R*,4*R*)-3-Hydroxy-4-aminopiperidine, ((–)-**8a**)**, dihydrobromide.** A stirred solution of **6a** (0.31g, 1 mmol) in methanol (15 mL) was hydrogenated at room temperature under atmospheric pressure with 10% Pd/C (0,03g) for 15 h ((monitored by TLC). Catalyst was filtered off and concentrated HBr was added up to pH 4. The solvent was then evaporated under reduced

pressure and the resulting salt was dried over NaOH and P_2O_5 in vacuo, and was recrystallized from iPrOH. Dihydrobromide of (–)-**8a,** white crystals, **(**0.24g, 87%**)**, mp 161-162 ºC, $[\alpha]_D^{20}$ **–** 19.2 (*c* 0.05, H_2O). Anal. Calcd for $C_5H_{12}Br_2N_2O$. C, 60.79; H, 8.59; N, 7.46. Found: C, 61.05; H, 8.50; N, 7.62. ^{1}H NMR (400MHz, D_2O), δ 1.95 (dddd, *J* 13.8, 13.3, 12.6, 4.3 Hz, 1H, H5$_a$), 2.41 (m, 1H, H5$_e$), 2.98 (dd, *J* 12.3, 11.1 Hz, 1H, H2$_a$), 3.15 (td, *J* 13.3, 3.0 Hz, 1H, H6$_a$), 3.42 (ddd, *J* 12.6, 10.4, 3.8 Hz, 1H, H4$_a$), 3.56 (br d, *J* 13.3 Hz, 1H, H6$_e$), 3.63 (ddd, *J* 12.3, 4.8, 1.0 Hz, 1H, H2$_e$), 3.99 (ddd, *J* 11.1, 10.4, 4.8 Hz, 1H, H3$_a$).

(+)-(3*S*,4*S*)-3-Hydroxy-4-aminopiperidine, ((+)-**8b**)**, dihydrobromide,** white crystals, **(**0.24g, 85%**)** was obtained similarly to (–)-**8a** by hydrogenolysis of **6b** (0.31g, 1 mmol) for 30 h at room temperature under atmospheric pressure with 10% Pd/C (0.03g), mp 159-160**º**C, $[\alpha]_D^{20}$ +18.9 (*c* 0.07, H_2O). Anal. Calcd for $C_5H_{12}Br_2N_2O$. C, 60.79; H, 8.59; N, 7.46. Found C 61.00, H 8.55, N 7.52. ^{1}H NMR spectra of (–)-**8a** and (+)-**8b** were identical.

The **salicylidenimine derivative** (–)-**9a** [or (+)-**9b**]. A mixture of aminoalcohol (–)-**8a** [or (+)-**8b**] (0,1g, 0.86 mmol) and salicylic aldehyde (0,11g, 0.89 mmol) in 15 mL absolute EtOH and toluene in ratio 2:1 was refluxed for 4 h. Solvents were evaporated under reduced pressure The remaining oil was dissolved in 10 mL $CHCl_3$ and after addition of 20 mL of hexane , the salicylidenimine derivative (–)-**9a** [or (+)-**9b**] was precipitated as a yellow solid, that was filtered off, washed with hexane and dried under vacuum. Yield: 0,09g (47%). ^{1}H NMR (400MHz, $CDCl_3$) δ 1.25 (m, 1H, H5$_a$), 2.10 (m, 1H, H5$_e$), 2.45-2.55 (m, 2H), 2.90 (m, 1H), 3.10-3.25 (m, 2H), 3.45 (m, 1H), 4.25 (br s, 2H, OH, NH), 6.55-6.70 (m, 3H, ArH, Ar-OH), 7.05-7.25 (m, 3H, ArH, CH=N). ^{13}C NMR (100MHz, $CDCl_3$) δ 31.3, 44.6, 51.2, 57.5, 71.3, 113.6, 113.8, 117.9, 128.0, 129.1, 147.4, 165.4.

Acknowledgements

This study was performed under financial support by the Russian Foundation for Basic Research (projects nos. 11-03-01034-a, 08-03-00266-a).

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