Chemistry of Heterocyclic Compounds, Vol. 48, No. 5, August, 2012 (Russian Original Vol. 48, No. 5, May, 2012)

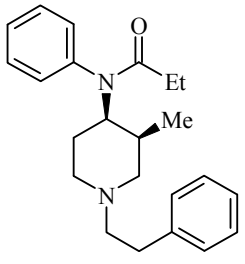
ASYMMETRIC SYNTHESIS AND STEREOCHEMISTRY OF CHIRAL *cis*- AND *trans*-3-ALKYL-4-AMINOPIPERIDINES

G. V. Grishina[1]*, E. R. Luk'yanenko[1], A. A. Borisenko[1], and M. Yu. Antipin[1]

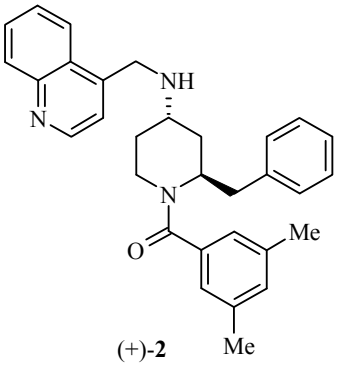
Chiral nonracemic 3-substituted cis- and trans-4-aminopiperidines, which are precursors of anilidopiperidine analgesics, were obtained by diastereoselective synthesis from 1-methyl- and 1-benzyl-4-[(S)-1-phenylethyl]iminopiperidines, using the following reaction sequence: metalation with lithium diethylamide, alkylation with alkyl halides, and hydride reduction or hydrogenation over Raney nickel. The steric direction of the reaction, three-dimensional structure, preferred conformation, and absolute configuration of the resultant aminopiperidines were determined.

Keywords: 3-alkyl-4-aminopiperidines, *cis* and *trans* isomers, conformational analysis, diastereomeric excess, diastereoselective synthesis, *Z-E* isomerism of imines.

Functional derivatives of piperidine, in particular, 4-aminopiperidines, occupy a special place among natural products and synthetic compounds with a broad spectrum of biological activity [1]. Despite the extensive information on the biological activity of 4-aminopiperidine derivatives, on which anilidopiperidine analgesics are based, there have been very few reports concerning the synthesis of chiral nonracemic 3-substituted 4-aminopiperidines. We should note that there is a strong relationship between analgesic activity and the absolute configuration of the stereogenic sites of 2- and 3-substituted 4-aminopiperidine derivatives. For example, the *in vivo* analgesic activity of the (+)-enantiomer of *cis*-3-methylfentanyl (+)-**1** is almost 120 times greater than that of the (-)-enantiomer, and 6846 times greater than the activity of morphine [1], while the *in vitro* activity of the strong selective neurokinin NK_1 receptor antagonist CGP 49823 (+)-**2** is 12 times greater than the activity of its (-)-enantiomer [2].



(+)-**1**



(+)-**2**

*To whom correspondence should be addressed, e-mail: grishina@org.chem.msu.ru.

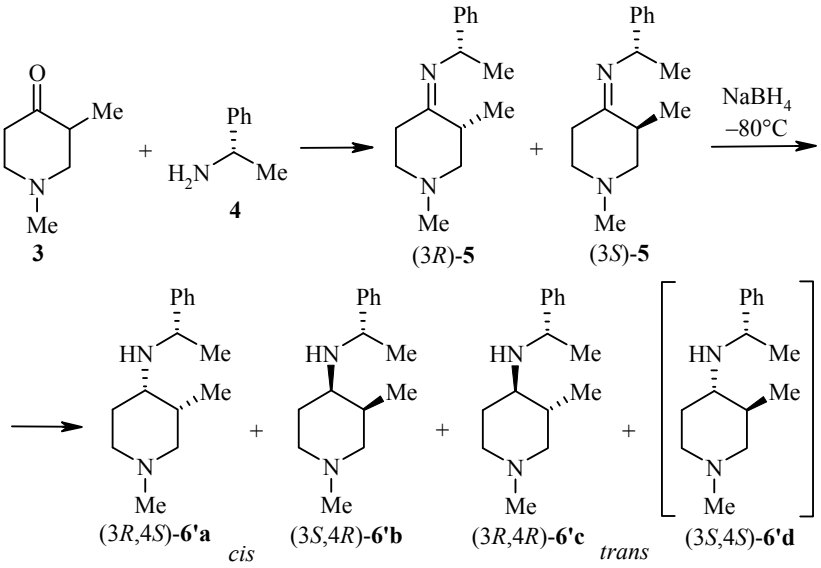
[1]M. V. Lomonosov Moscow State University, 1 Build. 3 Leninskie Gory, Moscow 119991, Russia.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 789-804, May, 2012. Original article submitted April 12, 2012.

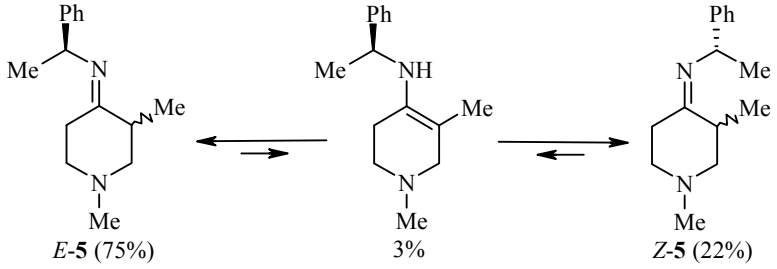
The lack of simple and efficient methods for obtaining optically pure 3-substituted 4-aminopiperidines is a serious obstacle to the study of the relationship between chirality and biological activity. The few reported optically active compounds of this class have been obtained by traditional separation of racemates. Only one example has been described in the literature for the efficient stereoselective synthesis of *cis*-(3*S*,4*R*)-4-amino-3-phenylpiperidine from the imine formed from 3-phenylpiperidin-4-one and (*R*)-1-phenylethylamine by hydrogenation of the imine over Raney nickel [3]. Thus, the development of a new diastereoselective synthetic pathway is extremely important for obtaining optically pure *cis* and *trans* isomers of 3-substituted 4-aminopiperidines.

In the present article, an effective strategy is presented for the preparation of chiral nonracemic *cis* and *trans* isomers of 3-substituted 4-aminopiperidines. A key point in this synthesis is the different steric direction of the reduction of *Z*- and *E*-forms of 3-alkylpiperidine imines. A preliminary brief communication on the reduction of the *Z*-form of 3-alkylpiperidine imines has already been published [4].

Imine **5** [5] was obtained for comparative experiments from 1,3-dimethylpiperidin-4-one (**3**) and (1*S*)-1-phenylethylamine (**4**). The formation of two *cis*- and *trans*-diastereomeric pairs of 1,3-dimethyl-4-[(*S*)-1-phe-nylethyl]aminopiperidine **6'a**,**b** and **6'c**,**d** in a 3:1 ratio has already been found in the asymmetric reduction of the 3-methylimine **5** with $NaBH_4$ in methanol. The diastereomeric excess (*de*) of the major isomers (**6'b** and **6'd**) in the *cis* and *trans* pairs was 62% and 74%, respectively [5].

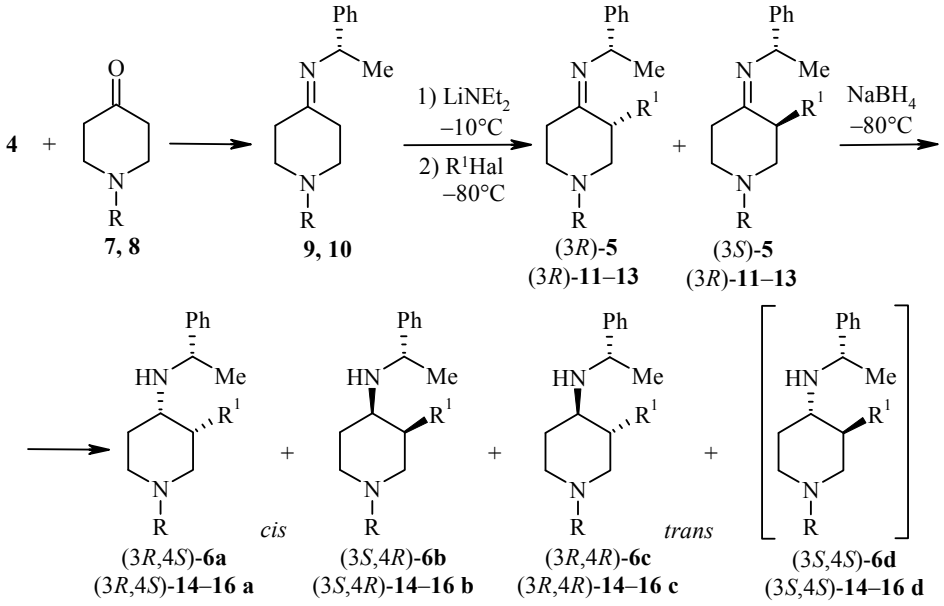


The moderate stereoselectivity in the reduction of the 3-methylimine **5** is a consequence of its complex isomeric and conformational composition. ^{1}H NMR spectroscopy indicates that the imine **5** is formed as a 1:1 mixture of (3*S*)- and (3*R*)-epimers, and there is a 22:75 *Z*-*E* equilibrium for each of the (3*S*)- and (3*R*)-epimers; the isomerization of these forms proceeds through an enamine [6].



Thus, a reduction of the individual *Z*- and *E*-forms of the 3-alkylimine **5** should improve the stereoselectivity of this reaction.

A reaction sequence without separation of intermediates was also carried out, involving lithiation of a 3-unsubstituted imine, alkylation of the azaenolate by an alkyl halide, and reduction of the 3-alkylated imine by $NaBH_4$ [4]. Optically active imines **9** and **10**, that were obtained from the reaction of (1*S*)-1-phenylethylamine (**4**) with 1-methyl- (**7**) and 1-benzylpiperidin-4-one (**8**), respectively, were selected as the starting compounds. As a result, a series of 1,3-disubstituted analogs **14-16** was obtained besides the amine **6**.



5, **6, 7**, **9**, **12**, **13**, **15**, **16** R = Me, **8**, **10**, **11**, **14** R = Bn;
5, **6**, **11**, **14** R^1 = Me, **12**, **15** R^1 = allyl, **13**, **16** R^1 = CH_2OMe

A ^{13}C NMR spectral study of the stereochemistry of the key intermediate – the alkylated imine, in which a new stereogenic site arises at C-3 with the formation of two *Z*-(3*S*)- and *Z*-(3*R*)-diastereomers, was carried out for the already reported imine **5**. Analysis of a reaction mixture sample 2 h after completion of the methylation reaction at 20°C indeed confirmed the formation of only the *Z*-(3*S*)- and *Z*-(3*R*)-forms of the 3-methylimine **5**, since two CH(Me)Ph carbon signals were observed at 65.6 and 65.7 ppm, respectively. Two new low-intensity ^{13}C NMR signals for the 1-phenylethyl substituent of the *E*-(3*S*)- and *E*-(3*R*)-forms were found at 64.9 and 65.0 ppm, respectively, after maintenance of the reaction mixture for 7 h at room temperature.

Leveling out of the carbon signal intensities from 1-phenylethyl substituents of the *Z*- and *E*-forms was observed only after 14 days, indicating a considerable kinetic stability of the *Z*-form of the 3-methylimine. The rate of the $Z \rightarrow E$ isomerization increases upon heating the reaction mixture to 50°C or upon removal of the solvent from the reaction mixture. The ^1H NMR spectrum indicates a ~3.5:1.0 equilibrium mixture of the *E*- and *Z*-isomers. Thus, the intermediate *Z*-form of the 3-substituted imine **5** has an entirely sufficient lifetime for completion of the reaction.

The predominant formation of the *Z*-imines is a consequence of the *syn* effect, which is due to the thermodynamic preference for formation of lithium azaenolate with *syn* orientation of the carbanion site and *N*-substituent, and the kinetic preference for retention of *syn* orientation of the alkylated α'-carbon atom and *N*-substituent in the alkylation reaction [7]. These conclusions are based on a ^{13}C NMR spectral study of the stereochemistry of cyclic ketone lithioimines and the products of their alkylation [8-11].

Thus, we have found that only the *Z*-(3*S*,*R*)-form of the 3-methylimine **5** undergoes hydride reduction. ^1H NMR signals at 0.85-1.05 ppm indicating three stereoisomers were found in the reaction mixture of the desired product, 1,3-dimethyl-4-aminopiperidine **6**. These signals were assigned to the 3-CH_3 groups of the *cis*

pair **6a,b** (0.94 ppm and 1.03 ppm, respectively) and to the 3-CH_3 group of the *trans* isomer **6c** (0.89 ppm), which is in good accord with our previous results [5]. We should also note the absence of the *trans* isomer **6d** in the reaction mixture, which will be discussed later in greater detail. Chromatography on an alumina column provided for separation of two individual compounds with R_f 0.2 and 0.6 (1:1 hexane–acetone), identified as the *trans*-**6c** and *cis*-**6a,b** isomers of the desired amine **6**, in accord with the chromatographic mobility of the *trans* and *cis* diastereomeric pairs of the amine **6'** [5]. The mass ratio of these two products was 1:1, and the total yield was 90%. The mass ratio of the pure isomers of amine **6a-c** was 0.64:0.36:1.00, which was virtually identical to their composition in the reaction mixture as indicated by ^{1}H NMR spectroscopy. The GC/MS of amine **6c** with R_f 0.2 also shows a single peak, while the nature of the decomposition of this compound upon electron impact is in accord with the structure of amine **6**.

The ^{1}H NMR spectrum of isomer **6c** corresponds to a single diastereomer (*de* > 98%), which was assigned as *trans* configuration in light of the vicinal $J_{3,4}$ coupling constant (12.0 Hz), indicating a diaxial arrangement of H-3 and H-4 protons and, thus, a diequatorial orientation of the 4-amino and 3-methyl groups. The *trans* orientation of the 4-amino and 3-methyl groups in the isomer **6c** was also indicated by the large coupling constants $J_{2,3}$ = 10.8 Hz and $J_{4,5}$ = 12.4 Hz. We should note that the chemical shift of the 3-CH_3 group protons in the isomer **6c** (0.89 ppm) is identical to the chemical shift given earlier for the minor *trans* amine **6'c** [4].

Two GC/MS peaks in a 1.76:1.00 ratio were found in the second product *cis*-**6a,b** with R_f 0.6. The mass-spectral decomposition of these peaks was virtually identical and corresponded to the structure of amine **6**. The *cis* pair **6a,b** and the *trans* amine **6c** have identical mass spectral fragmentation, differing only in the relative intensities of the characteristic ions with *m/z* 127, 111, 105, 96 and 84. The ^{1}H NMR spectrum of the *cis* pair **6a,b** has two sets of signals in a 1.80:1.00 ratio, which agrees with the GC/MS data. The low values of the vicinal coupling constants $J_{3,4}$ = 4.2 Hz and $J_{3,4}$ = 4.3 Hz, characteristic for an axial-equatorial interaction, correspond to a *cis* orientation of the H-3 and H-4 protons, and therefore a *cis* arrangement of the 4-amino and 3-methyl groups, that is, the pair of diastereomers **6a,b** has a *cis* structure.

A series of new 3-substituted 4-aminopiperidines **14-16** was synthesized under analogous conditions. The stereoisomers were isolated by column chromatography and their composition was supported by elemental analysis results, while their structure was established by ^{1}H NMR spectroscopy (Tables 1 and 2). Similar relations in isomeric composition, chromatographic mobility and three-dimensional structure were found among the isomers of the target amines **14-16**, as there were for the isomers of compound **6**.

^{1}H NMR spectroscopy indicated that all the isomers of **6c** and **14-16 c** have *trans* structure with equatorial orientation of the 3-alkyl and 4-*N*-(1-phenylethyl)amine groups in accord with the large vicinal coupling constants, $J_{3a,4a}$, $J_{2a,3a}$ and the small vicinal coupling constant, $J_{2e,3a}$. Furthermore, the chemical shift and multiplicity of the axial proton H-4 signal at 1.8 ppm (a triplet of doublets) proved to be a general criterion for assigning *trans* structures to all the isomers of **6c** and **14-16**. Individual *trans* amines **6c** and **14-16 c** were isolated with *de* > 98%.

The ^{1}H and ^{13}C NMR spectra of *cis*-**6a,b** and **14-16 a**,**b** are complicated by the existence of a conformational equilibrium, leading to broadening of the spectral lines. The *cis* orientation of the 4-*N*-substituent and the 3-alkyl group was established according to the vicinal coupling constants given in Table 2.

We should note that the ^{13}C NMR spectrum of the *trans* isomer **6c** indicates that this compound is conformationally homogeneous, while the low-temperature ^{13}C NMR spectrum of *cis* isomer **6a** shows that this compound exists as a conformational equilibrium (3*a*,4*e*)↔(3*e*,4*a*). A quantitative evaluation of this equilibrium is given in Table 3.

TABLE 1. Vicinal Coupling Constants (*J*, Hz) in the ^{1}H NMR Spectra of *trans*- Amines **6c** and **14-16 c**

Amine	$J_{3,4}$	$J_{4,5}$	Amine	$J_{3,4}$	$J_{4,5}$
6c	12.0	12.4	**15c**	11.9	11.9
14c	10.2	10.2	**16c**	10.2	10.2

TABLE 2. Vicinal Coupling Constants (J, Hz) in the ^{1}H NMR Spectra of *cis* Isomers **6a**,**b** and **14-16 a**,**b***

Amine	T, °C	$J_{3,4}$	$J_{2,3}$	$J_{4,5}$	Amine	T, °C	$J_{3,4}$	$J_{2,3}$	$J_{4,5}$
6a	20	4.2	—	7.1	**15a**	60	4.0	7.3	6.7
6b	40	4.3	5.0	9.1	**15b**	60	4.2	—	6.7
14a	20	4.2	—	6.7	**16a**	20	3.9	—	7.0
14b	20	4.1	—	8.7	**16b**	20	4.0	—	8.1

*The spectra of compounds **15a,b** were recorded in DMSO-d_6, while the spectra of the other compounds were recorded in $CDCl_3$.

TABLE 3. Chemical Shifts (δ, ppm) in the ^{13}C NMR Spectra of compounds *cis*-**6a** (Conformational Equilibrium (3*a*,4*e*)↔(3*e*,4*a*) at -65°C in CD_2Cl_2) and *trans*-**6c** (27°C)

Conformer (%)	C-2	C-3	C-4	C-5	C-6	1-CH_3	3-CH_3	$\underline{C}$H(Me)Ph	CH($\underline{C}H_3$)Ph
3*a*,4*e*-**6a** (62)	59.2	32.6	50.6	26.8	54.0	62.7	11.8	53.7	24.2
3*e*,4*a*-**6a** (38)	55.3	34.6	53.6	27.7	47.6	63.4	16.2	54.1	25.9
3*e*,4*e*-**6c** (100)	61.1	37.8	57.9	32.3	53.3	63.3	16.7	54.4	26.1

TABLE 4. Ratio and Diastereomeric Purity of *cis* and *trans* Isomers of the Amines **6** and **14-16**

Amine	Yield*, %	Ratio*[2] *cis* (**a** + **b**) / *trans* (**c**)	*de*[*3], %	
			cis-**a**	*trans*-**c**
6	90	1.0:1.0	28	>98
14	54	1.1:1.0	36	>98
15	81	1.9:1.0	38	>98
16	63	2.0:1.0	70	>98

*The total yield of *cis* and *trans* isomers after chromatographic separation.
*[2]Mass ratio after chromatographic isolation.
*[3]The *de* value for the *cis*-**a** isomers of amines **6**, **14**, and **15** was determined by GC/MS. The *de* for the *cis*-**a** isomer of amine **16** was determined by ^{1}H NMR spectroscopy. The *de* for the *trans*-**c** isomers of amines **6**, **14**, and **15** was determined by GC/MS and ^{1}H NMR spectroscopy. The *de* for the *trans*-**c** isomer of amine **16** was determined by ^{1}H NMR spectroscopy. The individual isomers **15a** and **15b** were isolated in a 2:1 ratio with *de* 98% and 90%, respectively.

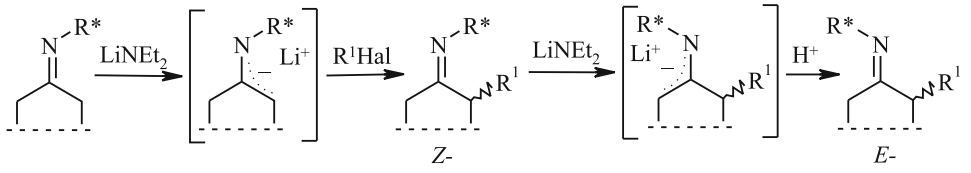
Isomers **14-16 a**,**b** were assigned to the *cis* series from an analysis of the multiplicity and chemical shift of the axial proton H-4. The ratio of the *cis* and *trans* isomers and the diastereomeric purity of isomers in the *cis* pairs of **a**,**b** are given in Table 4.

Antibatic steric direction of hydride reduction in the discussed reactions is noted from a comparison of the spectral data for the *cis* and *trans* isomer pairs of amine **6** and the previously described amine **6'**. Thus, for the major *cis* amine **6a**, the 3-CH_3 group proton doublet at 0.94 ppm coincides with the chemical shift of the 3-CH_3 protons of the minor component of the *cis* pair of the amine **6'a**, while the minor *cis* amine **6b** (1.03 ppm) corresponds to major *cis* isomer **6'b**.

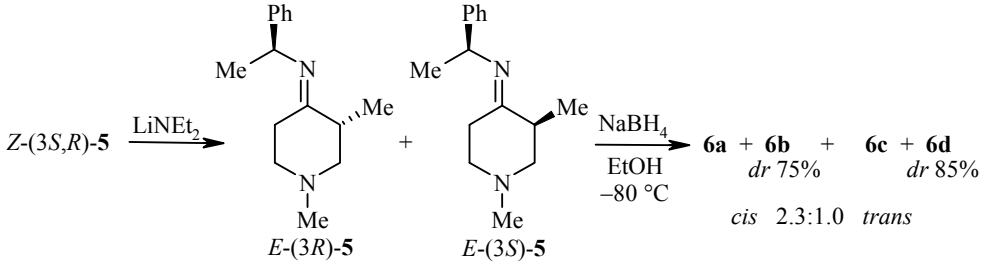
Thus, the proposed variant of the hydride reduction of the stereochemically pure *Z*-form of the 3-substituted imines gave diastereomerically pure *trans* amines **6, 14-16 c** with *de* > 98%, as well as diastereomerically enriched *cis* pairs of **6, 14-16 a**,**b** (with *de* up to 70%) of 3-substituted 4-aminopiperidines. Separation of the *cis* pairs of **15**, **16 a**,**b** was additionally carried out by crystallization of the hydrochlorides with subsequent ^{1}H NMR analysis of the free bases.

An axial orientation of the 3-methyl group was established in a ^{13}C NMR study of the stereochemistry of the (3*S*)- and (3*R*)-forms of intermediate *Z*-**5** by a double resonance technique. The ^{13}C NMR spectrum of the intermediate *Z*-**5** in THF at -78°C shows two C-4 signals at 170.5 and 170.9 ppm, corresponding to the *Z*-(3*S*)- and *Z*-(3*R*)-forms of intermediate *Z*-**5** in 2.3:1.0 ratio. A *cis* pair arises from an axial hydride attack on the prochiral C=N bond of each *Z*-form: the major isomer *cis*-**6a** and the minor isomer *cis*-**6b**. In this case, the major *cis* isomer of **6a** is formed from the more reactive *Z*-form of intermediate **5**. In the case of an equatorial hydride attack of the C=N bond, one *trans* isomer of **6c** is formed. The second *trans* isomer of **6d**, which should also arise upon equatorial hydride attack, is not formed due to the different reactivity of the *Z*-(3*S*)- and *Z*-(3*R*)-forms of the intermediate **5**. Analogous behavior is seen in the entire series of *trans* isomers of **14-16 c**.

The synthetic potential of the *Z*-form of the 3-substituted imines was expanded due to the "switch" of the α-alkylated *Z*-imines to α'-alkylated *E*-imines, which occurs upon repeated lithiation of the *Z*-form of the imine at the α'-position.



Relithiation of the 3-methylimine *Z*-**5** was carried out by the action of three equivalents of lithium diethylamide at 20°C for 2 h. Hydrolysis of the obtained lithioimine and reduction of the resulting imine *E*-**5** were carried out by a consecutive addition of a solution of three equivalents of triethylammonium hydrochloride in 20 equivalents absolute ethanol and one equivalent of $NaBH_4$ at -80°C.



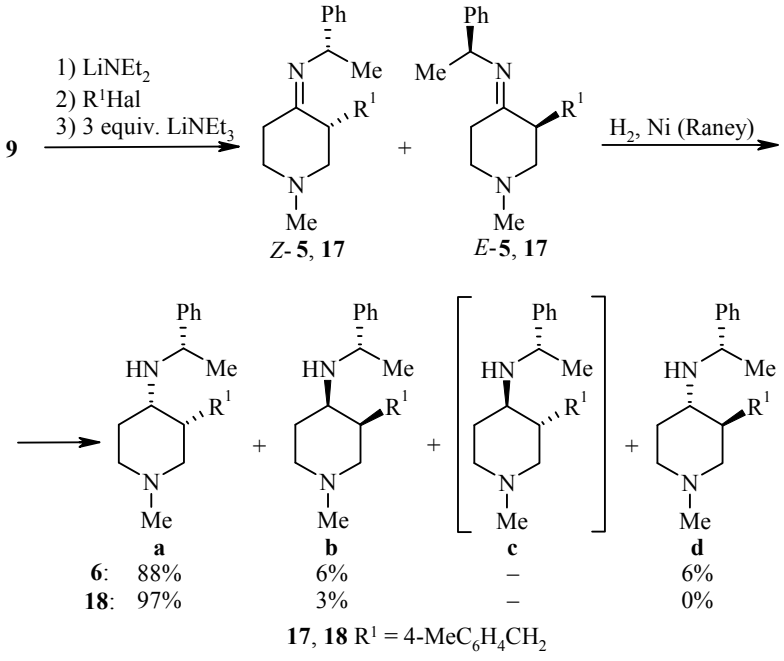
Indeed, the ^{13}C NMR spectrum of intermediate **5** sample after relithiation showed four species: *E*-(3*S,R*) (C-4, 169.8, 170.0 ppm) and *Z*-(3*S,R*) (C-4, 170.5, 170.9 ppm) in a ~3.5:1.0 ratio. The significant changes in the stereochemical composition are a consequence of the transformation of the *Z*-imine to the *E*-imine.

Hydride reduction and chromatographic separation gave *cis* pair **6a,b** and *trans* pair **6c,d** in 95% total yield. From ^{1}H NMR spectrum data, the major form in the *cis* pair **6a,b** proved to be the isomer **6b** with *de* 75%, which was established from the integral intensity ratio of the doublets of the 3-CH_3 group protons in isomers **6a** (0.94 ppm) and **6b** (1.03 ppm). Analogously, the integral intensity ratio of the doublets of the 3-CH_3 groups in *trans* isomers **6c** (0.89 ppm) and **6d** (0.99 ppm) gave *de* for the major isomer **6d**, equal to 85%. The large vicinal coupling constants ($J_{3,4} = J_{4,5} = 11.7$ Hz, $J_{2a,3a} = 11.3$ Hz) confirm the *trans* structure of amine **6d**, whose conformational equilibrium is completely shifted toward the 3*e*,4*e*-conformer.

Thus, a difference is noted in the steric direction of the hydride reduction of imine *E*-**5** compared to the stereochemistry of the reduction of imine *Z*-**5**. The isomers *cis*-**6b** and *trans*-**6d** proved predominant in the amine **6**. These results indicate that $Z \rightarrow E$ isomerization of 3-methylimine **5** upon relithiation proceeds with a high degree of conversion.

Dynamic kinetic resolution with predominant formation of the *cis* amine **6a** with *de* > 98% occurs upon hydrogenation of the equilibrium relithiated mixture of *E*- and *Z*-(3*S,R*)-3-methylimines **5** over 120 h in the presence of freshly-prepared Raney nickel (W4 activity) in ethanol at a 20 atm hydrogen pressure and 20°C. The reaction end-point was determined by ^{1}H NMR spectra of reaction mixture samples, by disappearance of the 3-methyl group signals from the imine **5**.

At the end of the hydrogenation reaction, the ^{1}H NMR spectrum of the reaction mixture showed 88% *cis* isomer **6a**, 6% *cis* isomer **6b**, and 6% *trans* isomer **6d**. Pure *cis* amine **6a** was isolated from the reaction mixture as dihydrobromide in a 55% yield. ^{1}H NMR spectroscopy indicated that the *de* value for amine **6a** after crystallization from a mixture of absolute ethanol and ether was >98%. Alkylation of the imine **9** with 4-methylbenzyl chloride and subsequent relithiation gave also the *Z*- and *E*-forms of 4-imino-3-(4-methylbenzyl)piperidine **17**. The hydrogenation of these compounds was carried out over seven days at 40°C with a smaller amount of catalyst (0.5 g Raney nickel per 10 mmol of imine) and 5 atm pressure. ^{1}H NMR spectroscopy of the reaction mixture indicated that the *de* value for the desired product, *cis*-3-(4-methylbenzyl)piperidine-4-amine **18a** was 97% (~3% of the *cis* isomer **18b**). Similarly, ^{1}H NMR spectra of the *cis* amine **18a** dihydrobromide indicated that this product was obtained with *de* > 98% and 47% yield.



Thus, all four imine forms (*Z*-(3*S*,3*R*) and *E*-(3*S*,3*R*)) in a dynamic equilibrium due to interconversion through an enamine species are present in the reaction mixture during the optically pure 3-substituted 4-aminopiperidine preparation sequence entailing lithiation, alkylation, and hydrogenation over Raney nickel [6]. Under the catalysis conditions, the most reactive intermediate, *Z*-(3*R*)-**5**, is reduced significantly faster than the other forms, which accelerates the conversion of the other intermediates into this more reactive species, as the hydrogenation progresses, i.e., dynamic kinetic separation occurs in this process. Such an approach has been used by Frahm et al. in the preparation of various *cis*-1-amino-2-substituted cycloalkanes with high diastereomeric purity [12-16].

The absolute configuration of the *cis* amine **18a** dihydrobromide was established as (α*S*,3*R*,4*S*) by X-ray structural analysis (Fig. 1) using a 1-phenylethyl substituent with (*S*)-configuration as a chiral label. The piperidine ring is in virtually ideal "chair" conformation with axial arrangement of the substituent at the C(3) atom and equatorial orientation of the substituent at the C(4) atom.

Thus, the *Z*-(3*R*)-form proved the most reactive of the four forms of diastereomeric intermediates **17**, which also leads exclusively to the optically pure *cis*-(3*R*,4*S*)-amine **18a**. This result helps to clarify the hydride reduction stereochemistry of intermediate *Z*-(3*R*)-**5**. As shown above, the major *cis* amine **6a** with (3*R*,4*S*)-configuration is formed from the intermediate *Z*-(3*R*)-**5** upon axial hydride attack (*ax*) on the prochiral C=N bond, while the *cis*-(3*R*,4*S*)-amine **6b** is formed from intermediate *Z*-(3*S*)-**5**. In the case of equatorial hydride attack (*eq*) of the C=N bond, the *trans* isomer **6c**, whose absolute configuration should be (3*R*,4*R*), would be formed from intermediate *Z*-(3*R*)-**5**.

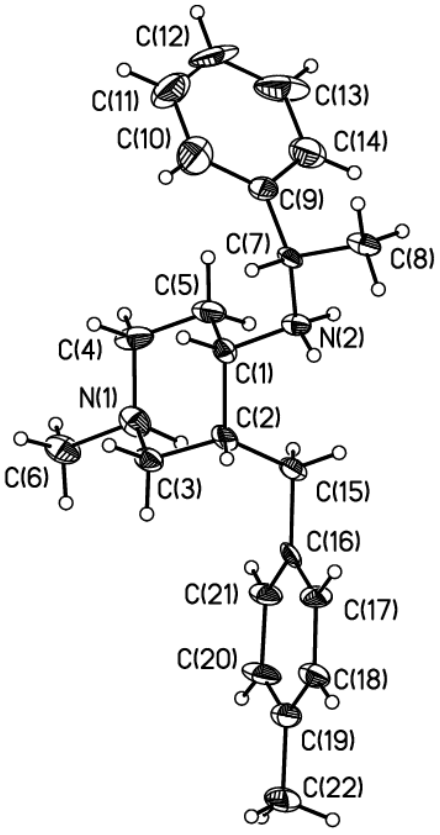
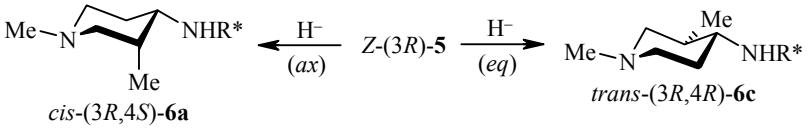


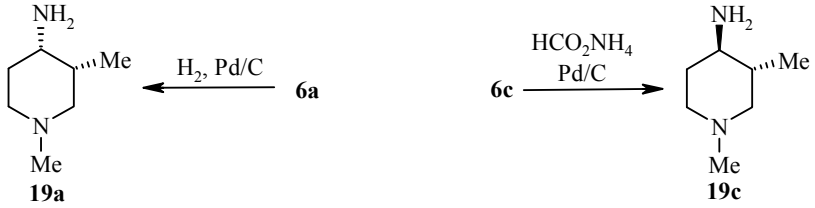
Fig. 1. General view of *cis*-(3*R*,4*S*)-1-methyl-3-(4-methylbenzyl)-*N*-[(1*S*)-phenylethyl]piperidin-4-amine (**18a**). The atoms are shown as 50%-probability thermal vibration ellipsoids.



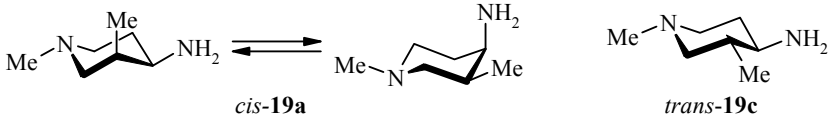
cis-(3*R*,4*S*)-**6a** *trans*-(3*R*,4*R*)-**6c**

Thus, the entire series of *cis* amines **14-16 a** also has (3*R*,4*S*)-configuration. The major isomer *cis*-(3*S*,4*R*)-**6b** and minor isomer *cis*-(3*R*,4*S*)-**6a** are formed from intermediate *E*-(3*R,S*)-**5** upon axial hydride attack on the prochiral imine C=N bond, while equatorial hydride attack on the C=N bond leads to the major isomer *trans*-(3*S*,4*S*)-**6d** and minor isomer *trans*-(3*R*,4*R*)-**6c**.

When the chiral (*S*)-1-phenylethyl group is removed by hydrogenolysis in the presence of Pd/C, the optically pure *cis* isomer **6a** and *trans* isomer **6c** also give optically pure isomers of 1,3-dimethylpiperidin-4-amine, *cis*-(3*R*,4*S*)-(**19a**) and *trans*-(3*R*,4*R*)-(**19c**), which were isolated as dihydrochloride salts in 73% and 56% yields, respectively.



The composition of the obtained isomeric amines **19a,c** was confirmed by elemental analysis. The configuration of the stereogenic sites at C-3 and C-4 in isomers **19a** and **19c** was not altered during the hydrogenolysis. The *trans* structure of isomer **19c**, which exists exclusively as the 3*e*,4*e*-conformer, was indicated by the large values of the vicinal coupling constants in the ^{1}H NMR spectra ($J_{3,4}$ = 11.9 Hz, $J_{2,3}$ = 11.1 Hz and $J_{4,5}$ = 11.9 Hz). The *cis* structure of isomer **19a**, which exists in a conformational equilibrium 3*a*,4*e* ⇌ 3*e*,4*a*, follows from the values of the vicinal coupling constants ($J_{3,4}$ = 7.6 Hz and $J_{4,5}$ = 6.5 Hz).



cis-**19a** *trans*-**19c**

The absolute configuration of (+)-*cis*-(3*R*,4*S*)-1,3-dimethylpiperidin-4-amine (**19a**) was additionally confirmed by comparison of the signs of specific rotation for this isomer and its stereochemical analog (-)-*cis*-(3*S*,4*R*)-3-methyl-4-phenylpiperidinamine with a known absolute configuration [1]. The opposite signs of their specific rotation indicate opposite configurations of the compounds compared.

Thus, a simple, highly-stereoselective sequence entailing metalation, alkylation, and hydride reduction of imines obtained from piperidin-4-ones and the (*S*)- or (*R*)-enantiomers of 1-phenylethylamine leads to the formation of various optically pure *trans*-3-substituted 4-aminopiperidines. An asymmetrical synthesis was developed for optically pure 3-substitited *cis*-4-aminopiperidines by a reaction sequence involving metalation, alkylation, and Raney nickel hydrogenation of 3-substituted 4-iminopiperidines. The steric direction of these reactions and the absolute configuration were determined for the whole series of optically pure *cis* and *trans* isomers of 3-substituted 4-aminopiperidines.

EXPERIMENTAL

The IR spectra were recorded neat on a UR-20 spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian XL-400 spectrometer at 400 MHz and 100 MHz, respectively. The conformational analysis of compounds *cis*-**6a** and *trans*-**6c** was carried out on a Bruker DRX-500 spectrometer at 500 MHz for the ^{1}H NMR spectra and at 125 MHz for the ^{13}C NMR spectra with TMS as internal standard. The GC/MS data were obtained on an HP-5890 Series II instrument with direct sample inlet using a 30 m×0.25 mm HP-5MS column packed with SPB-5 reverse phase. The high-resolution mass spectrum was recorded on

TABLE 5. Major Bond Lengths (*l*) in Compound **18a** Molecule

Bond	*l*, Å	Bond	*l*, Å
N(1)–C(4)	1.488(13)	C(2)–C(3)	1.515(14)
N(1)–C(6)	1.513(14)	C(9)–C(10)	1.410(2)
N(1)–C(3)	1.520(14)	C(10)–C(11)	1.390(2)
N(1)–H(1N1)	1.0877	C(11)–C(12)	1.370(3)
N(2)–C(1)	1.496(12)	C(12)–C(13)	1.380(2)
N(2)–C(7)	1.552(11)	C(13)–C(14)	1.369(18)
N(2)–H(1N2)	0.8437	C(15)–C(16)	1.538(13)
N(2)–H(2N2)	0.9601	C(16)–C(21)	1.377(14)
C(1)–C(5)	1.541(15)	C(17)–C(18)	1.396(18)
C(1)–C(2)	1.548(13)	C(19)–C(20)	1.383(16)
C(2)–C(15)	1.535(14)	C(20)–C(21)	1.409(13)
C(5)–C(1)	1.493(3)	C(22)–H(22)	0.9600
C(1)–O(1)	1.197(2)	C(1S)–C(2S)	1.27(3)
C(4)–C(5)	1.511(16)	C(1S)–H(1SA)	0.9700
C(7)–C(9)	1.499(18)	C(2S)–H(2SA)	0.9600
C(7)–C(8)	1.513(14)	C(2S)–H(2SB)	0.9600
C(2S)–H(2SC)	0.9600	O(1W)–H(1W)	0.0802

TABLE 6. Major Valence Angles (ω) in Compound **18a** Molecule

Angle	ω, deg.	Angle	ω, deg.
C(4)–N(1)–C(6)	111.3(9)	C(1)–N(2)–H(1N2)	116.6 (7)
C(4)–N(1)–C(3)	109.7(8)	C(7)–N(2)–H(1N2)	113.9
C(6)–N(1)–C(3)	111.8(9)	C(1)–N(2)–H(1N2)	96.2
C(4)–N(1)–H(1N1)	114.4(15)	C(7)–N(2)–H(2N2)	109.8
C(6)–N(1)–H(1N1)	106.3	C(4)–N(1)–H(2N2)	109.4
C(3)–N(1)–H(1N1)	103.2	N(2)–C(1)–C(5)	113.1(8)
C(1)–N(2)–C(7)	116.9	N(2)–C(1)–C(2)	110.4(8)
C(5)–C(1)–H(1)	107.2	C(8)–C(7)–N(2)	110.7(8)
C(2)–C(2)–H(1)	107.2	C(9)–C(7)–H(7)	107.5
C(3)–C(2)–C(15)	114.6(9)	H(SA)–C(1S)–H(1SB)	110.4
C(3)–C(2)–C(1)	106.8(8)	C(1S)–C(2S)–H(2SA)	109.5
C(9)–C(7)–N(2)	111.1(8)	C(1S)–C(2S)–H(2SC)	109.5
H(2SA)–C(S)–H(2SB)	109.5	H(2SA)–C(2S)–H(2SC)	109.5
C(1S)–C(2S)–H(2SB)	109.5	H(2SB)–C(2S)–H(2SC)	109.5
H(1W)–O(1W)–H(2W)	106.4	O(1S)–C(1S)–H(1SB)	113.0

a JEOL AccuTOF instrument. The specific rotation $[\alpha]_D^{20}$ was determined on a Perkin Elmer 241 polarimeter with a 0.25-dm cell. The concentration is indicated in g/100 cm^3. Thin layer chromatographic analysis was carried out on Merck Silufol plates for compounds **19a,c** and Alufol plates for the other compounds. The elemental analysis was carried out on a Vario MICRO cube CPNS analyzer. Column chromatography was carried out on neutral Merck alumina. The metalation reaction and subsequent alkylation of the imines were carried out in an argon atmosphere. Imine **5** for the comparative experiments was obtained according to our previous procedure [5], the physicochemical and spectral data corresponded to the literature values [5].

(1*S*)-*N*-(1-Methylpiperidin-4-ylidene)-1-phenylethylamine (9) and (1*S*)-*N*-(1-benzylpiperidin-4-ylidene)-1-phenylethylamine (10) were obtained according to our previous procedure [17] in 90% and 98% yields, respectively. The analytical data for imine **9** match the literature [17]. **Imine 10:** n_D^{20} 1.5634, $[\alpha]_D^{20}$ -40° (*c* 3.8, C_6H_6). IR spectrum, cm^{-1}: 1680 (C=N). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.46 (3H, d, *J* = 7.0, CH(C<u>H</u>$_3$)Ph); 2.47-2.50 (8H, m, 2,3,5,6-CH_2); 3.53 (2H, s, CH_2Ph); 4.30 (1H, q, *J* = 7.0, C<u>H</u>(Me)Ph); 7.26-7.29 (5H, m, H Ph). Found, *m/z*: 293.3996 $[M+H]^+$. $C_{19}H_{24}N_2$, Calculated, *m/z*: 292.4080.

TABLE 7. Major Torsion Angles (θ) in Compound **18a** Molecule

Angle	θ, deg.	Angle	θ, deg.
C(7)–N(2)–C(1)–C(5)	90.3(10)	C(8)–C(7)–C(9)–C(10)	-117.9(11)
C(7)–N(2)–C(1)–C(2)	-144.0(8)	N(2)–C(7)–C(9)–C(10)	117.6(11)
N(2)–C(1)–C(2)–C(3)	176.7(8)	C(8)–C(7)–C(9)–C(14)	57.7(13)
C(5)–C(1)–C(2)–C(2)	-56.7(11)	N(2)–C(7)–C(9)–C(14))	-66.8(13)
N(2)–C(1)–C(2)–C(15)	70.8(12)	C(14)–C(9)–C(10)–C(11)	2.4(16)
C(15)–C(2)–C(3)–N(1)	-68.7(11)	C(7)–C(9)–C(10)–C(11)	178.2(11)
C(1)–C(2)–C(3)–N(1)	58.4(10)	C(9)–C(10)–C(11)–C(12)	-2.0(2)
C(4)–N(1)–C(3)–C(2)	-61.7(11)	C(10)–C(11)–C(12)–C(13)	1.0(2)
C(6)–N(1)–C(3)–C(2)	174.4(8)	C(7)–C(9)–C(14)–C(13)	178.0(10)
C(3)–N(1)–C(4)–C(5)	60.2(12)	C(1)–C(2)–C(15)–C(16)	177.6(9)
N(1)–C(4)–C(5)–C(1)	-58.6(12)	C(2)–C(15)–C(16)–C(17)	-81.4(12)
N(2)–C(1)–C(5)–C(4)	-177.1(8)	C(21)–C(16)–C(17)–C(18)	-1.8(16)
C(2)–C(1)–C(5)–C(4)	57.8(11)	C(17)–C(16)–C(21)–C(20)	3.9(16)
C(1)–N(2)–C(7)–C(9)	-62.4(12)	C(15)–C(16)–C(21)–C(20)	-177.4(10)
C(1)–N(2)–C(7)–C(8)	172.2(8)	C(19)–C(20)–C(21)–C(16)	-3.6(18)

Hydride Reduction of *Z*-(3*S*,*R*)-forms of Imines 5, 11-13. The *cis* and *trans* Isomers of 1,3-Dialkylpiperidin-4-yl-*N*-[(1*S*)-1-phenylethyl]amines 6, 14-16 a-c (General Method) (see also our previous work [4]). A solution of imine **9** or **10** (3.00 g, 13.9 mmol) in absolute THF (5 ml) was added over 10 min with stirring at -10°C to a solution of $LiNEt_3$ obtained from $HNEt_2$ (1.32 g, 18.0 mmol) in absolute THF (20 ml) and 1.6 N BuLi (11.3 ml, 18.0 mmol) in hexane. The reaction mixture was stirred for 30 min at -10°C. After cooling to -80°C, alkyl halide (18.0 mmol) was added, and the reaction mixture was stirred for 30 min. Then, absolute ethanol (2 ml) and $NaBH_4$ (0.50 g, 13.9 mmol) were added consecutively. The reaction mixture was stirred for 1 h at -80°C and then brought to room temperature. The solvents were distilled off in vacuum. The residue was decomposed by carefully adding 6 N hydrochloric acid and then 10 ml water. The reaction mixture was brought to pH 12 by adding 20% aqueous NaOH and extracted with methylene chloride (2×30 ml). The organic extracts were combined and dried over anhydrous sodium sulfate. The solvent was evaporated. The residue was subjected to chromatography on an alumina column with gradient elution using 30:1 to 1:1 hexane–ethyl acetate.

The reaction of imine **9** with MeI gave 1.42 g (44%) of the *cis* pair (3*R*,4*S*)-**6a** and (3*S*,4*R*)-**6b**, R_f 0.6, and 0.68 g (21%) of the *trans* isomer (3*R*,4*R*)-**6c**, R_f 0.2. The R_f values were obtained with a 1:1 hexane–acetone eluent. An analytical sample of isomers **6a,b** was separated by GC/MS, and the obtained spectral data corresponded to the literature values [4]. **Dipicrate of *trans* isomer 6c** was obtained by mixing ethereal solutions of the amine **6c** and picric acid. The precipitate obtained was filtered off and recrystallized from ethanol. Found, %: C 47.10; H 4.37; N 16.06. $C_{15}H_{24}N_2 \cdot 2C_6H_3N_3O_7$. Calculated, %: C 46.96; H 4.38; N 16.23. Treatment of the amine **6c** dipicrate with aqueous potassium carbonate and subsequent extraction with ether gave the free base of *trans* isomer **6c** with *de* > 98%, as indicated by ^{1}H NMR spectroscopy. The spectral and analytical data corresponded to the literature values [4].

***cis*- and *trans*-1-Benzyl-3-methylpiperidin-4-yl-*N*-[(1*S*)-1-phenylethyl]amine (14).** Isomers of the amine **14** were obtained in a similar way from the imine **10** and MeI. Chromatographic separation gave 0.34 g (8%) of the *cis* isomer (3*R*,4*S*)-**14a** (*de* 90%, GC/MS), 0.84 g (20%) of the *cis* isomer (3*S*,4*R*)-**14b** (*de* 98%, GC/MS) and 1.10 g (26%) of the *trans* isomer (3*R*,4*R*)-**14c** (*de* > 98%, ^{1}H NMR, GC/MS). ***cis* Isomer 14a:** R_f 0.8 (2:1 hexane–acetone), $[\alpha]_D^{20}$ -31.6° (*c* 3.48, C_6H_6). ^{1}H NMR spectrum (C_6D_6), δ, ppm (*J*, Hz): 0.97 (3H, d, *J* = 6.8, 3-CH_3); 1.23 (3H, d, *J* = 6.6, CH(C<u>H</u>$_3$)Ph); 1.54-1.57 (2H, m, H-3*e*,5*a*); 1.73-1.75 (1H, m, H-5*e*); 2.40-2.43 (2H, m, H-2*a*,6*a*); 2.70-2.71 (1H, m, H-2*e*); 2.46 (1H, ddd, $J_{3e,4a}$ = 4.0, $J_{4a,5e}$ = 4.0, $J_{4a,5a}$ = 8.0, H-4*a*); 2.51-2.53 (1H, m, H-6*e*); 3.27 (2H, dd, *J* = 13.2, CH_2Ph); 3.74 (1H, q, *J* = 6.8, C<u>H</u>(Me)Ph); 7.10-7.40 (10H, m, H Ph). Mass-spectrum (τ 16.30 min), *m/z* (I_{rel}, %): 308 $[M]^+$ (<1), 203 $[M\text{-}CH(CH_3)C_6H_5]^+$ (62), 105 $[CH(CH_3)C_6H_5]^+$ (31), 91 $[CH_2C_6H_5]^+$ (100). ***cis* Isomer 14b:** R_f 0.75, $[\alpha]_D^{20}$ -69.6° (*c* 3.16, C_6H_6). ^{1}H NMR

spectrum (CD_2Cl_2), δ, ppm (*J*, Hz): 1.05 (3H, d, *J* = 6.9, 3-CH_3); 1.20 (3H, d, *J* = 6.6, CH(C<u>H</u>$_3$)Ph); 1.33-1.35 (1H, m, H-5*e*); 1.49-1.51 (1H, m, H-5*a*); 1.75-1.77 (1H, m, H-6*a*); 1.86-1.87 (1H, m, H-3*e*); 2.29-2.31 (1H, m, H-2*e*); 2.41-2.43 (1H, m, H-2*a*,6*a*); 2.40 (1H, ddd, $J_{3e,4a}$ = 4.1, $J_{4a,5e}$ = 4.1, $J_{4a,5a}$ = 8.7, H-4*a*); 2.51-2.53 (1H, m, H-6*e*); 3.17 (2H, dd, *J* = 13.3, CH_2Ph); 3.71 (1H, q, *J* = 6.5, C<u>H</u>(Me)Ph); 7.10-7.40 (10H, m, H Ar). Mass-spectrum (τ 16.11 min), *m/z* (I_{rel}, %): 308 $[M]^+$ (<1), 203 $[M\text{-}CH(CH_3)C_6H_5]^+$ (79), 105 $[CH(CH_3)C_6H_5]^+$ (33), 91 $[CH_2C_6H_5]^+$ (100). ***trans* Isomer 14c:** R_f 0.5, $[\alpha]_D^{20}$ -63.2° (*c* 8.29, C_6H_6). ^{1}H NMR spectrum (C_6D_6), δ, ppm (*J*, Hz): 0.88 (3H, d, *J* = 6.5, 3-CH_3); 1.18 (3H, d, *J* = 6.5, CH(C<u>H</u>$_3$)Ph); 1.37 (1H, d, $J_{2a,3a}$ = 10.7, H-2*a*); 1.49-1.50 (1H, m, H-5*a*); 1.51-1.53 (1H, m, H-3*a*); 1.59 (1H, ddd, $J_{6a,6e}$ = 11.7, $J_{6a,5a}$ = 11.7, $J_{6a,5e}$ = 2.5, H-6*a*); 1.80 (1H, ddd, $J_{4a,3a}$ = 10.2, $J_{4a,5a}$ = 10.2, $J_{4a,5e}$ = 4.1, H-4*a*); 1.93-1.95 (1H, m, H-5*e*); 2.68-2.69 (1H, m, H-2*e*); 2.73-2.76 (1H, m, H-6*e*); 3.26 (2H, s, CH_2Ph); 3.84 (1H, q, *J* = 6.5, C<u>H</u>(Me)Ph); 7.05-7.25 (10H, m, H Ph). Mass spectrum (τ 16.28 min), *m/z* (I_{rel}, %): 308 $[M]^+$ (<1), 203 $[M\text{-}CH(CH_3)C_6H_5]^+$ (22), 105 $[CH(CH_3)C_6H_5]^+$ (27), 91 $[CH_2C_6H_5]^+$ (100). **Dipicrate of the diastereomer mixture 14a-c** was obtained analogously to the dipicrate of amine **6c**, mp 235-236 °C (EtOH). Found, %: C 51.59; H 4.39; N 14.37. $C_{21}H_{28}N_2 \cdot 2C_6H_3N_3O_7$. Calculated, %: C 51.70; H 4.47; N 14.62.

***cis*- and *trans*-3-Allyl-1-methylpiperidin-4-yl-*N*-[(1*S*)-1-phenylethyl]amine (15).** Stereoisomers of amine **15** were obtained analogously from the imine **9** and allyl bromide. Chromatographic separation gave 1.83 g (51%) of the *cis* diastereomer pair (3*R*,4*S*)-**15a** and (3*S*,4*R*)-**15b** and 0.96 g (27%) of the *trans* isomer (3*R*,4*R*)-**15c**. The *cis* pair: R_f 0.7 (1:1 hexane–acetone), $[\alpha]_D^{20}$ -47.0° (*c* 2.0, benzene). Isomer **15a** (*de* 38%, GC/MS) predominates in the *cis* pair. ***cis* Isomer 15a**: ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.23-1.24 (1H, m, H-5*a*); 1.29 (3H, d, *J* = 7.1, CH(C<u>H</u>$_3$)Ph); 1.51-1.57 (2H, m, H-3*e*,2*a*); 1.64-1.71 (2H, m, H-6*a*, C<u>H</u>$_A$H$_B$CH=CH$_2$); 1.72 (1H, ddd, $J_{4a,3a}$ = 10.0, $J_{4a,5a}$ = 10.0, $J_{4a,5e}$ = 3.7, H-4*a*); 2.03-2.05 (1H, m, H-5*e*); 2.22 (3H, s, 1-CH_3); 2.74-2.80 (3H, m, H-2*e*,6*e*, CH$_A$<u>H</u>$_B$CH=CH$_2$); 3.82 (1H, q, *J* = 7.1, CH(Me)Ph); 5.65-5.67 (2H m, CH$_2$CH=C<u>H</u>$_2$); 5.85-5.87 (1H, m, CH$_2$C<u>H</u>=CH$_2$); 7.10-7.35 (5H, m, H Ph). Mass spectrum (τ 14.53 min), *m/z* (I_{rel}, %): 258 $[M]^+$ (1), 153 $[M\text{-}CH(CH_3)C_6H_5]^+$ (73), 105 $[CH(CH_3)C_6H_5]^+$ (61), 96 (100). ***cis* Isomer 15b:** ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.27-1.29 (1H, m, H-5*a*); 1.31 (3H, d, *J* = 7.1, CH(C<u>H</u>$_3$)Ph); 1.33 (3H, d, *J* = 6.0, 3-CH_3); 1.46-1.53 (2H, m, H-2*a*,3*e*); 1.63-1.77 (2H, m, H-6*a*, C<u>H</u>$_A$H$_B$CH=CH$_2$); 1.84 (1H, ddd, $J_{4a,3a}$ = 11.9, $J_{4a,5a}$ = 11.9, $J_{4a,5e}$ = 3.7, H-4*a*); 2.12 (1H, m, H-5*e*); 2.17 (3H, s, 1-CH_3); 2.65-2.70 (1H, m, CH$_A$<u>H</u>$_B$CH=CH$_2$); 2.74-2.80 (2H, m, H-2*e*,6*e*); 3.80 (1H, q, *J* = 7.1, CH(Me)Ph); 4.94-5.00 (2H, m) and 5.65-5.69 (1H, m, CH=C<u>H</u>$_2$); 5.70-5.72 (1H, m, CH$_2$C<u>H</u>=CH$_2$); 7.10-7.35 (5H, m, H Ph). Mass spectrum (τ 14.60 min), *m/z* (I_{rel}, %): 258 $[M]^+$ (1), 153 $[M\text{-}CH(CH_3)C_6H_5]^+$ (58), 105 $[CH(CH_3)C_6H_5]^+$ (57), 96 (100). ***trans* Isomer 15c:** *de* > 98%, R_f 0.3 (1:1 hexane–acetone), $[\alpha]_D^{20}$ -57° (*c* 2.0, C_6H_6). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.40-1.50 (2H, m, H-2*a*,3*a*); 1.45-1.48 (1H, m, H-5*a*); 1.66-1.77 (2H, m, H-6*a*, C<u>H</u>$_A$H$_B$CH=CH$_2$); 1.84 (1H, ddd, $J_{4a,3a}$ = 10.2, $J_{4a,5a}$ = 10.2, $J_{4a,5e}$ = 3.7, H-4*a*); 2.12-2.14 (1H, m, H-5*e*); 2.65-2.69 (1H, m, CH$_A$<u>H</u>$_B$CH=CH$_2$); 2.74-2.80 (2H, m, H-2*e*,6*e*); 3.96 (1H, q, *J* = 6.6, CH(Me)Ph); 4.94-5.00 (2H, m) and 5.70-5.73 (1H, m, CH=CH$_2$); 7.20-7.35 (5H, m, H Ph). Mass spectrum (τ 4.60 min), *m/z* (I_{rel}, %): 258 $[M]^+$ (2), 153 $[M\text{-}CH(CH_3)C_6H_5]^+$ (26), 105 $[CH(CH_3)C_6H_5]^+$ (38), 96 (100). **Dipicrate of *trans* isomer 15c** was obtained analogously to dipicrate of the amine **6c**. Found, %: C 48.45; H 4.48; N 15.67. $C_{17}H_{26}N_2 \cdot 2C_6H_3N_3O_7$. Calculated, %: C 48.61; H 4.50; N 15.64.

***cis*- and *trans*-1-Methyl-3-(methoxymethyl)piperidin-4-yl-*N*-[(1*S*)-1-phenylethyl]amine (16).** Stereoisomers of the amine **16** were obtained by an analogous procedure from the imine **9** and chloromethyl methyl ether. Chromatographic separation gave 1.53 g (42%) of the *cis* diastereomer pair (3*R*,4*S*)-**16a** and (3*S*,4*R*)-**16b**, and 0.76 g (21%) of the *trans* isomer (3*R*,4*R*)-**16c**. Isomer **16a** (*de* 71%, ^{1}H NMR) predominates in the *cis* pair. ***cis* Isomer 16a:** R_f 0.65 (1:1 hexane–acetone), $[\alpha]_D^{20}$ -33.0° (*c* 4.0, PhMe). ^{1}H NMR spectrum (DMSO-d_6, 60 °C), δ, ppm (*J*, Hz): 1.26 (3H, d, *J* = 6.6, CH(C<u>H</u>$_3$)Ph); 1.48-1.53 (2H, m, H-3*e*,5*a*); 1.71-1.73 (1H, m, H-5*e*); 2.11 (3H, s, 1-CH_3); 2.32-2.40 (2H, m, H-2*a*,6*a*); 2.51-2.57 (1H, m, H-6*e*); 2.65 (1H, ddd, $J_{3e,4a}$ = 3.9, $J_{4a,5e}$ = 3.9, $J_{4a,5a}$ = 7.1, H-4*a*); 2.73-2.80 (1H, m, H-2*e*); 3.20 (3H, s, OCH_3); 3.42 (2H, dd, *J* = 7.8, *J* = 4.4, CH_2OMe); 3.81 (1H, q, *J* = 6.6, CH(Me)Ph); 7.16-7.35 (5H, m, H Ph). ***cis* Isomer 16b**: ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.31 (3H, d, *J* = 6.5, CH(C<u>H</u>$_3$)Ph); 1.58-1.60 (2H, m, H-3*e*,5*a*); 1.68-1.72

(1H, m, H-5*e*); 2.23 (3H, s, 1-CH_3); 2.30-2.35 (2H, m, H-2*a*,6*a*); 2.46-2.48 (1H, m, H-6*e*); 2.60 (1H, ddd, $J_{3e,4a}$ = 3.9, $J_{4a,5e}$ = 3.9, $J_{4a,5a}$ = 7.0, H-4*a*); 2.68-2.70 (1H, m, H-2*e*); 3.29 (3H, s, OCH_3); 3.45 (2H, dd, *J* = 9.7, *J* = 4.8, CH_2OMe); 3.80 (1H, q, *J* = 6.5, CH(Me)Ph); 7.58-7.75 (5H, m, H Ph). **Dihydrobromide of isomers 16a,b** was obtained by adding a solution of the isomers **16a,b** in ether to a saturated solution of HBr in ether at 0°C. The precipitate formed was filtered off, dried in vacuum over P_2O_5 and then over NaOH, and recrystallized from absolute ethanol. Found, %: C 45.40; H 6.34; N 5.97. $C_{16}H_{26}N_2O\cdot 2HBr$. Calculated, %: C 45.48; H 6.20; N 6.62. ***trans* Isomer 16c:** *de* > 98% (^{1}H NMR spectrum), R_f 0.35 (1:1 hexane–acetone), *dr* > 98% (^{1}H NMR spectrum), R_f 0.35 (hexane–acetone, 1:1), $[\alpha]_D^{20}$ -81.0° (*c* 3.7, PhMe). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.31 (3H, d, *J* = 6.6, CH(C<u>H</u>$_3$)Ph); 1.29 (1H, ddd, $J_{5a,4a}$ = 11.9, $J_{5a,6a}$ = 9.4, $J_{5a,6e}$ = 3.7, H-5*a*); 1.36-1.39 (1H, m, H-3*a*); 1.58 (1H, d, $J_{2a,3a}$ = 11.0, H-2*a*); 1.89-1.92 (1H, m, H-4*a*); 1.99 (1H, dd, $J_{6a,5a}$ = 9.4, $J_{6a,5e}$ = 4.1, H-6*a*); 2.12 (1H, ddd, $J_{5e,4a}$ = 2.3, $J_{5e,6a}$ = 4.1, $J_{5e,6e}$ = 3.6, H-5*e*); 2.19 (3H, s, 1-CH_3); 2.76 (1H, dd, $J_{6e,5a}$ = 3.7, $J_{6e,5e}$ = 3.6, H-6*e*); 2.83 (1H, dd, $J_{2e,3a}$ = 3.8, $J_{6e,2e}$ = 1.9, H-2*e*); 3.20 (1H, dd, *J* = 9.7, *J* = 6.2) and 3.53 (1H, dd, *J* = 9.7, *J* = 4.8, CH_2OMe); 3.30 (3H, s, OCH_3); 3.93 (1H, q, *J* = 6.6, CH(Me)Ph); 7.19-7.35 (5H, m, H Ph). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 25.7; 31.8; 42.1; 46.2; 53.7; 54.1; 54.7; 58.3; 58.7; 74.2; 126.5, 126.6, 128.2, 146.0. Mass spectrum, *m/z* (I_{rel}, %): 262 $[M]^+$ (<5), 157 $[M\text{-}CH_3CHC_6H_5]^+$ (37), 105 $[CH_3CHC_6H_5]^+$ (100).

Hydride Reduction of the *E*-(3*S*,*R*) Form of Imine 5. The *cis* and *trans* Isomers of 1,3-dimethylpiperidin-4-yl-*N*-[(1*S*)-1-phenylethyl]amine (6). Methyl iodide was added to a solution of 3-methylimine **5** obtained as described in the general method above, and the reaction mixture was maintained for 30 min at -10°C. The mixture was then cooled to -30°C, and a solution of lithium diethylamide, obtained from $HNEt_2$ (4.10 g, 56 mmol) and 1.6 N BuLi in hexane (35 ml, 56 mmol), in absolute THF (50 ml) was added. The reaction mixture was stirred for 45 min at -30°C, and then 45 min at 25°C. The mixture was cooled to -80°C, and absolute ethanol (3 ml) and $NaBH_4$ (0.68 g, 18 mmol) were added. The mixture was stirred for 1 h at -80°C, and then allowed to warm to room temperature with vigorous stirring. The solvents were removed in vacuum, and the residue was decomposed by carefully adding 6 N hydrochloric acid until hydrogen no longer evolved. Then water (10 ml) was added. The mixture was brought to pH 12 by adding 20% aqueous NaOH and extracted with CH_2Cl_2 (2×30 ml). The organic extracts were combined and dried over anhydrous sodium sulfate. The solvent was evaporated in vacuum. The residue was subjected to chromatography on an alumina column with gradient elution from 30:1 to 1:1 hexane–ethyl acetate. The R_f values of isomers **6a-d** are given above. This procedure gave 2.02 g (68%) of the *cis* pair (3*R*,4*S*)-**6a** and (3*S*,4*R*)-**6b** with predominance of the isomer **6b** (*de* 69%), and 0.80 g (25%) of the *trans* pair (3*R*,4*R*)-**6c** and (3*S*,4*S*)-**6d** with predominance of the isomer **6d** (*de* 87%). The *cis* pair: $[\alpha]_D^{20}$ -48° (*c* 2.0, benzene; The *trans* pair: $[\alpha]_D^{20}$ +1° (*c* 5.9, toluene). **The *trans* isomer 6d:** ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.99 (3H, d, *J* = 6.4, 3-CH_3); 1.26-1.28 (1H, m, H-5*a*); 1.29 (3H, d, *J* = 6.4, CH(C<u>H</u>$_3$)Ph); 1.54 (1H, ddd, $J_{3a,2a}$ = 10.8, $J_{3a,4a}$ = 11.7, $J_{3a,2e}$ =3.4, H-3*a*); 1.63 (1H, d, $J_{2a,3a}$ = 10.8, H-2*a*); 1.73 (1H, ddd, $J_{5e,4a}$ = 2.6, $J_{5e,6a}$ = 4.0, $J_{5e,6e}$ = 3.3, H-5*e*); 1.81 (1H, ddd, $J_{4a,3a}$ = 11.7, $J_{4a,5a}$ = 11.7, $J_{4a,5e}$ = 2.6, H-4*a*); 2.01 (1H, dd, $J_{6a,5a}$ = 10.1, $J_{6a,5e}$ = 4.0, H-6*a*); 2.19 (3H, s, 1-CH_3); 2.68-2.75 (2H, m, H-2*e*,6*e*); 3.86 (1H, q, *J* = 6.4, CH(Me)Ph); 7.17-7.34 (5H, m, H Ph). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 16.5; 23.9; 33.1; 37.8; 46.0; 55.2; 56.2; 58.8; 63.0; 126.4; 126.5; 128.1; 147.0.

***cis*-(3*R*,4*S*)-1-Methyl-3-(4-methylbenzyl)piperidin-4-yl-*N*-[(1*S*)-1-phenylethyl]amine (18a).** A solution of imine **9** (3.00 g, 13.9 mmol) in absolute THF (5.0 ml) was added at -10°C with stirring over 10 min to a solution of $LiNEt_2$ obtained from $HNEt_2$ (1.32 g, 18.0 mmol) in absolute THF (20 ml) and 1.6 N solution of BuLi in hexane (11.3 ml, 18.0 mmol). The reaction mixture was stirred for 30 min at -10°C and then cooled to -80°C. 4-MeC_6H_4Cl (2.56 g, 18.0 mmol) was added. The obtained solution was stirred at -10°C for 30 min and then cooled to -30°C. A solution of lithium diethylamide, obtained from Et_2NH (4.10 g, 56.0 mmol) and 1.6 N BuLi in hexane (35.0 ml, 56.0 mmol), in absolute THF (50 ml) was then added. The reaction mixture was left to warm to room temperature with stirring. The solvent was distilled off. The residue was dissolved in absolute ethanol (20 ml), and Raney nickel (W4 activity), freshly prepared from Ni/Al alloy (2.8 g) was added. The reaction mixture was then hydrogenated for seven days at 5 bar hydrogen pressure and 40°C. The catalyst was

filtered off, and the solvent was evaporated. Then, 5% aqueous NaOH (20 ml) was added to the residue, and the mixture was extracted with CH_2Cl_2 (2×30 ml). The organic extracts were combined and dried over anhydrous sodium sulfate. The solvent was evaporated. The residue was dissolved in ethanol (10 ml) and brought to pH ~3 by adding concentrated hydrobromic acid. The solution was evaporated. The residue was dried in vacuum over P_2O_5, and then over NaOH. Crystallization from 2:1 ethanol–ether gave 3.00 g (47%) of the *cis*-(3*R*,4*S*)-isomer **18a** dihydrobromide with *de* > 98%, mp 222-224°C. Isolation of the free base of *cis* isomer **18a**: a solution of **18a** dihydrobromide (0.135 g, 0.3 mmol) in water (1 ml) was brought to pH 10 by adding aqueous potassium carbonate and extracted with CH_2Cl_2 (4×3 ml). The combined extract was dried over anhydrous sodium sulfate. The solvent was evaporated in vacuum and the residue was dried in vacuum at 40°C for 30 min, to give 0.090 g (74%) of the *cis* isomer **18a** as a viscous oil, $[\alpha]_D^{20}$ -106° (*c* 2.5, EtOH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.18 (3H, d, *J* = 7.0, CH(C<u>H</u>$_3$)Ph); 2.26 (3H, s, 1-CH_3); 2.75 (1H, dd, $J_{4e,3a}$ = 7.6, $J_{4e,5a}$ = 6.5, H-4*e*); 1.33-1.35 (1H, m, H-5*a*); 1.36-1.39 (1H, m, H-3*a*); 1.66-1.69 (1H, m, H-6*a*); 2.02 (1H, d, $J_{4a,5e}$ = 6.5, H-4*a*); 2.08-2.10 (1H, m, H-5*e*); 2.85-2.89 (2H, m, H-2*e*,6*a*); 7.30-7.40 (9H, m, H Ar). Found, %: C 81.74; H 9.21; N 8.74. $C_{22}H_{30}N_2$. Calculated, %: C 81.94; H 9.38; N 8.69.

***cis* Isomer 6a dihydrobromide** was obtained in a similar manner to the previous procedure, by using methyl iodide (1.1 ml, 2.56 g, 18.0 mmol) as the alkylating agent. The hydrogenation was carried out in the presence of Raney nickel obtained from Ni/Al alloy (3.00 g) over 120 h at 20 bar hydrogen pressure and room temperature. **Isomer 6a dihydrobromide**: yield 3.01 g (55%); mp 210-212°C (EtOH). The free base of isomer **6a** was isolated from its dihydrobromide salt (0.12 g, 0.3 mmol) analogously to the previous procedure. Yield 0.04 g (55%). The physicochemical and spectral data of this product correspond to the literature values [4].

(+)-*cis*-(3*R*,4*S*)-1,3-Dimethylpiperidin-4-ylamine (19a). A solution of the *cis*-(3*R*,4*S*)-isomer **6a** (1.18 g, 5.1 mmol) in ethanol (20 ml) was hydrogenated over 10% Pd/C (0.40 g) for 24 h at 1 bar hydrogen pressure and 20°C. The catalyst was filtered off. The solution was brought to pH ~3.5 by adding a saturated solution of hydrogen chloride in methanol. The solvents were removed by evaporation. The residue was dried in vacuum over P_2O_5 and then NaOH. The obtained precipitate was crystallized from 2:1 absolute ethanol–ether to give 0.75 g (73%) of *cis*-(3*R*,4*R*)-1,3-dimethyl-4-aminopiperidine (**19a**) dihydrochloride, mp 156-157°C, $[\alpha]_D^{20}$ -12° (*c* 8.6, H_2O). The free base of the amine **19a** was isolated from its dihydrochloride (0.75 g) in water (2 ml) by adding dry potassium carbonate to bring the solution to pH 9. The mixture was extracted with CH_2Cl_2 (2×2 ml) and dried over sodium sulfate. The solvent was evaporated in vacuum to give the amine **19a.** Yield 0.40 g (84%). Colorless oil, R_f 0.4 (CH_2Cl_2–MeOH, 3:1 + 0.1% NH_3), $[\alpha]_D^{20}$ -43° (*c* 5.3, C_6H_6). ^{1}H NMR spectrum (DMSO-d_6, 60°C), δ, ppm (*J*, Hz): 0.87 (3H, d, *J* = 7.0, 3-CH_3); 2.08 (1H, dd, $J_{3a,2a}$ = 10.8, $J_{2e,3a}$ =3.9, H-2*e*); 1.29 (2H, s, NH_2); 1.37-1.49 (1H, m, H-5*a*); 1.53 (1H, ddd, $J_{3a,2e}$ = 2.1, $J_{3a,2a}$ = 10.8, $J_{3a,4a}$ = 12.0, H-3*a*); 2.11 (3H, s, 1-CH_3); 2.20 (1H, d, $J_{2a,3a}$ = 7.6 H-2*a*); 2.39-2.41 (1H, m, H-6*e*); 2.75 (1H, dd, $J_{4e,3a}$ = 3.8, $J_{4e,5a}$ = 3.8, H-4*e*); 2.85-2.91 (2H, m, H-6*a*,5*e*). ^{13}C NMR spectrum (DMSO-d_6, 60°C), δ, ppm: 13.3; 31.5; 34.3; 45.8; 48.4; 51.5; 58.5. **Amine 19a dihydrochloride**. Found, %: C 41.63; H 9.28; N 13.94. $C_7H_{16}N_2$·2HCl. Calculated, %: C 41.80; H 9.02; N 13.93.

(-)-*trans*-(3*R*,4*R*)-1,3-Dimethylpiperidin-4-ylamine (19c). 10% Pd/C (0.40 g) and dry ammonium formate (7.38 g, 117.0 mmol) in three portions of 2.46 g each were added consecutively to a solution of the *trans*-(3*R*,4*R*)-isomer **6c** (0.91 g, 3.9 mmol) in methanol (15 ml), and the obtained mixture was heated at reflux for 2 h until the complete disappearance of ammonium formate. The reaction end-point was determined by thin-layer chromatography by the disappearance of the spot for isomer **6c**. The catalyst was filtered off and the reaction solution was brought to pH ~3.5 by adding a saturated solution of hydrogen chloride in methanol. The solvents were evaporated. The residue was dried in vacuum over P_2O_5, and then over NaOH. The residue was crystallized to give 0.44 g (56%) of the *trans*-(3*R*,4*R*)-1,3-dimethylpiperidin-4-ylamine (**19c**) dihydrochloride, mp 229-231°C (2:1 abs. ethanol–ether), $[\alpha]_D^{20}$ -17° (*c* 3.3, H_2O). The free base of the amine **19c** was isolated similarly to the isomer **19a**, R_f 0.3 (CH_2Cl_2–MeOH, 3:1 + 0.1% NH_3), $[\alpha]_D^{20}$ -28° (*c* 1.6, MeOH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.94 (3H, d, *J* = 6.7, 3-CH_3); 1.26 (2H, s, NH_2); 1.37-1.49 (2H, m, H-3*a*,5*a*); 1.62 (1H, d, $J_{2a,3a}$ = 11.1, H-2*a*); 1.80 (1H, ddd, $J_{5e,4a}$ = 2.6, $J_{5e,6e}$ = 2.6, $J_{5e,6a}$ = 4.4, H-5*e*); 1.95 (1H, ddd,

$J_{4a,3a}$ = 11.9, $J_{4a,5a}$ = 11.9, $J_{4a,5e}$ = 2.6, H-4*a*); 2.17 (1H, dd, $J_{6a,5a}$ = 9.7, $J_{6a,5e}$ = 4.1, H-6*a*); 2.25 (3H, s, N-CH_3); 2.75 1H, d, $J_{2e,3a}$ = 3.8, H-2*e*); 2.84-2.89 (1H, m, H-6*e*). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 16.3; 29.7; 35.6; 39.7; 46.1; 55.5; 62.7. Found, %: C 41.67; H 9.17; N 13.99. $C_7H_{16}N_2 \cdot 2HCl$. Calculated, %: C 41.80; H 9.02; N 13.93.

X-ray Structural Study of 18a Dihydrobromide. Monoclinic crystals of compound **18a** were grown in ethanol ($C_{24}H_{40}Br_2N_2O_2$, *M* 548.40). Unit cell parameters at 173 K: *a* = 12.771(7), *b* = 7.393(3), *c* = 14.160(6) Å, β = 90.94(4)°, *V* = 1336.8(11) Å^3, space group $P2_1$, *Z* = 2, d_{calc} = 1.362 g/cm^3, μ(MoKα) = 30.53 mm^{-1}, *F*(000) = 568. A total of 3663 reflections were measured on a Syntex 2_1 four-circle diffractometer (MoKα, graphite monochromator, θ/2θ scanning, θ_{max} = 28.06°), of which 3442 independent reflections (R_{int} = 0.0268) were used to decipher and refine the structure. The structure was deciphered by the direct method and refined relative to F^2 by the full-matrix method of least squares in the anisotropic-isotropic approximation. The hydrogen atoms were located from the difference maps for the solvate water and ethanol molecules and calculated for the dication using the "horse-rider" model. The final probability factors were: wR_2 = 0.1927 over all the reflections, R_1 = 0.0778 and *GOOF* = 0.972 (for 2067 reflections). The complete crystallographic data were deposited at the Cambridge Crystallographic Data Center (CCDC 882510). The major interatomic distances, bond and deformation angles are given in Tables 5-7.

This work was carried out with the financial support of the Russian Foundation for Basic Research (projects 8-03-0026a and 11-03-01034a).

REFERENCES

1. W. F. M. van Bever, C. J. E. Niemegeers, and P. A. J. Janssen, *J. Med. Chem.*, **17**, 1047 (1974).
2. S. Ofner, K. Hauser, W. Schilling, A. Vassout, and S. J. Veenstra, *Bioorg. Med. Chem. Lett.*, **6**, 1623 (1996).
3. D. Flockerzi, V. Figala, H. Amschler, and G. Hummel, DE Pat. Appl. DE4217401. *Chem. Abstr.*, **118**, 254760 (1993).
4. G. V. Grishina, E. L. Gaidarova, and E. R. Luk'yanenko, *Khim. Geterotsikl. Soedin.*, 622 (2004) [*Chem. Heterocycl. Compd.*, **40**, 525 (2004)].
5. G. V. Grishina and E. L. Gaidarova, *Khim. Geterotsikl. Soedin.*, 1072 (1992). [*Chem. Heterocycl. Compd.*, **28**, 898 (1992)].
6. G. V. Grishina, E. L. Gaidarova, and A. E. Aliev, *Khim. Geterotsikl. Soedin.*, 1369 (1992). [*Chem. Heterocycl. Compd.*, **28**, 1166 (1992)].
7. R. R. Frazer, J. Banville, and K. L. Dhawan, *J. Am. Chem. Soc.*, **100**, 7999 (1978).
8. A. I. Meyers, D. R. Williams, G. W. Erickson, S. White, and M. Druelinger, *J. Am. Chem. Soc.*, **103**, 3081 (1981).
9. S. Mangelinckx, N. Giubellina, and N. De Kimpe, *Chem. Rev.*, **104**, 2353 (2004).
10. R. R. Frazer and N. Chuaqui-Offermanns, *Can. J. Chem.*, **59**, 3007 (1981).
11. R. R. Frazer and J. Banville, *J. Chem. Soc., Chem. Commun.*, No. 1, 47 (1979).
12. W. Wiehl and A. W. Frahm, *Chem. Ber.*, **119**, 2668 (1986).
13. F. Omar and A. W. Frahm, *Arch. Pharm.*, **322**, 461 (1989).
14. A. W. Frahm and G. Knupp, *Tetrahedron Lett.*, **22**, 2633 (1981).
15. G. Lauktien, F.-J. Volk, and A. W. Frahm, *Tetrahedron: Asymmetry*, **8**, 3457 (1997).
16. L. K. Liem and A. W. Frahm, *Arch. Pharm.*, **324**, 335 (1991).
17. G. V. Grishina, V. P. Potapov, and S. A. Abdulganeeva, *Chem. Heterocycl. Comp.*, 372 (1986). [*Chem. Heterocycl. Compd.*, **22**, 304 (1986)].