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Synthesis of Stereodefined Piperidines from Aziridines and Their Transformation into Conformationally Constrained Amino Acids, Amino Alcohols and 2,7-Diazabicyclo[3.3.1]nonanes

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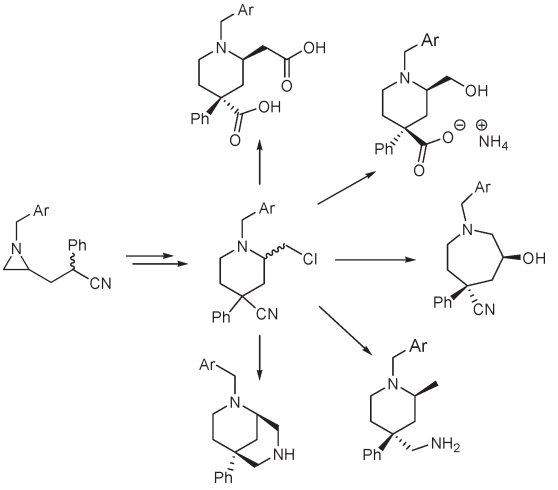

2-(2-Cyano-2-phenylethyl)aziridines were converted into novel *cis*- and *trans*-2-chloromethyl-4-phenylpiperidine-4-carbonitriles *via* alkylation with 1-bromo-2-chloroethane followed by microwave-assisted 6-*exo*-*tet* cyclization and regiospecific ring opening. The latter piperidines were used as eligible substrates for the synthesis of stereodefined 2-chloromethyl-, 2-hydroxymethyl-, and 2-carboxymethyl-4-phenylpiperidine-4-carboxylic acids, 2-hydroxymethyl-4-phenylpiperidine-4-carbonitriles, 3-hydroxy-5-phenylazepane-5-carbonitriles, and 5-phenyl-2,7-diazabicyclo[3.3.1]nonanes.

Introduction

The piperidine ring comprises an important structural unit in natural products and biologically active agents, and several thousands of piperidine compounds have been evaluated in clinical and preclinical studies.[1] For these reasons, the search for general, efficient, and stereoselective methods for piperidine synthesis has attracted the attention of the organic chemistry community for many years.[2] In particular, 4-arylpiperidines represent an interesting class of biologically relevant compounds, about which numerous examples can be found in the patent literature.[3] 4-Arylpiperidines are known to be useful as for example tachykinin antagonists for the treatment of pain and inflammation,[4] and as α-1a adrenergic receptor antagonists for the treatment of prostate disorders.[5]

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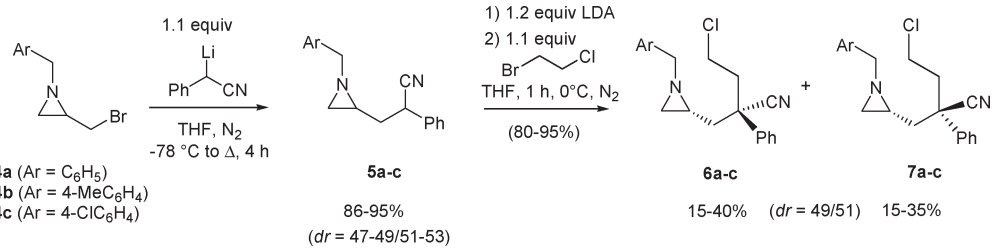
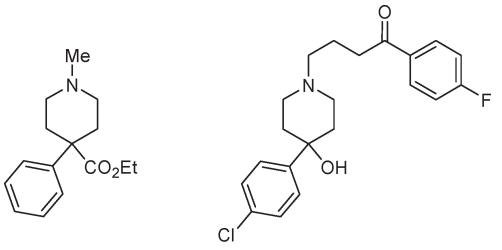
SCHEME 1



Moreover, a number of drugs each accommodates a 4-arylpiperidine unit in its structure, such as the analgesic meperidine **1** and the antipsychotic haloperidol **2**.[6]



Meperidine 1 **Haloperidol 2**

From a synthetic point of view, aziridines have proven to be excellent precursors for the preparation of functionalized piperidines. Indeed, intramolecular ring opening of aziridines by a remote amino moiety[7] and ring opening using Grignard reagents followed by elaboration of the tethered side chain[8] are known strategies for the synthesis of piperidines starting from aziridines. Alternatively, [3+3]-cycloadditions of Pd−trimethylenemethane complexes with enantiomerically pure aziridines,[9] and aza-[2,3]-Wittig rearrangements of vinylaziridines[10] have also been used successfully in that respect.

In this paper, an efficient and direct method toward the novel 2-chloromethyl-4-phenylpiperidine-4-carbonitrile scaffold is presented starting from 2-(2-cyano-2-phenylethyl)-aziridines. Piperidine-4-carbonitriles were employed successfully as substrates for the synthesis of a wide variety of stereodefined piperidines ranging from γ-amino acids and adipic acid derivatives to bicyclic piperidines with biological interest.

Results and Discussion

The chemistry of 2-(2-cyanoethyl)aziridines remains an underexplored field of research, as only a few examples have been reported so far.[11] Nevertheless, their synthetic usefulness has been demonstrated recently through the development of a versatile aziridine-to-cyclopropane ring transformation.[12] In continuation of our interest in 2-(cyanoalkyl)-aziridines[12,13] as substrates in organic chemistry, a new protocol for the conversion of 2-(2-cyanoethyl)aziridines into functionalized piperidines was developed.

1-Arylmethyl-2-(bromomethyl)aziridines, **4**, prepared from the corresponding benzaldehydes in a three-step procedure,[14] are known to be excellent substrates for the synthesis of a variety of 2-substituted 1-(arylmethyl)aziridines.[12,15] Thus, 2-(bromomethyl)aziridines **4** were treated with 1.1 equiv of α-lithiated phenylacetonitrile in THF, affording 2-(2-cyano-2-phenylethyl)aziridines, **5**, as mixtures of diastereomers in good yields.[12b] With the intention to introduce a 2-chloroethyl group in the α-position with respect to the nitrile moiety in aziridines **5**, the coupling between 1-bromo-2-chloroethane and aminonitriles **5** was accomplished using 1.2 equiv of lithium diisopropylamide (LDA) in THF, furnishing novel 4-chloro-2-[1-(arylmethyl)aziridin-2-ylmethyl]-2-phenylbutyronitriles **6** and **7** as a mixture of diastereomers ($\sim$1/1) after one hour at 0 °C (Scheme 1). Interestingly, diastereomers **6** could be easily isolated from the mixtures by crystallization from ethanol (15−40% yield), and diastereomers **7** were obtained in pure form through column chromatography on silica gel (hexane/EtOAc, 3:1, 15−35% yield), allowing their full spectroscopic characterization.

The incorporation of a leaving group in the ε-position with regard to the aziridine nitrogen atom renders aziridines **6** and **7** excellent substrates for a 6-*exo*-*tet* ring closure toward intermediate bicyclic aziridinium salts, suitable for further elaboration. It should be noted that the α-alkylation of nitriles using 2-chloro-1-haloethanes has scarcely been reported in the literature.[16]

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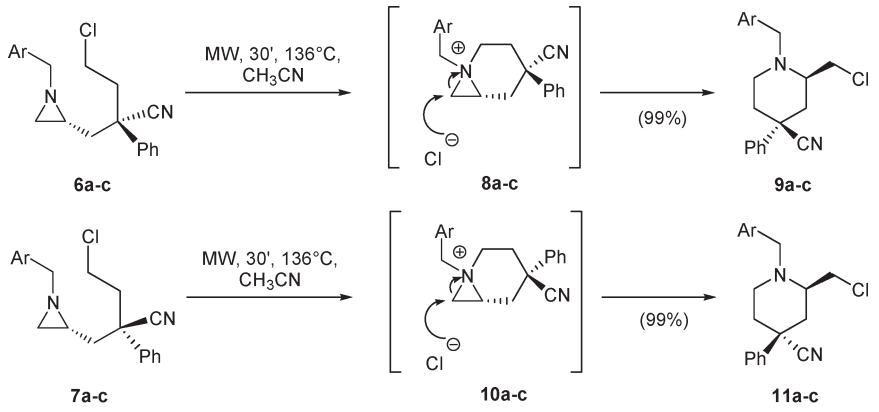
SCHEME 2



a: Ar = C_6H_5, **b**: Ar = 4-MeC_6H_4, **c**: Ar = 4-ClC_6H_4

Interestingly, when heated under reflux in THF, no cyclization of aziridines **6** and **7** toward piperidines took place. Clearly, a more polar solvent had to be used to allow intramolecular substitution and to stabilize the intermediate bicyclic aziridinium ions. In accordance with the previously reported ring-opening reactions of nonactivated aziridines with benzyl bromide,[12,15d,17] acetonitrile was used as a solvent, and the premised 6-*exo*-*tet* ring-expansion reaction of aziridines **6** and **7** proceeded nicely under microwave irradiation at 136 °C for 30 min or, alternatively, in DMSO for 3 h under reflux applying conventional heating, affording 2-chloromethyl-4-phenylpiperidine-4-carbonitriles **9** and **11** in excellent yields and purity (Scheme 2). The proposed mechanism involves an intramolecular substitution reaction, furnishing bicyclic aziridinium intermediates **8** and **10**, followed by regiospecific ring opening by chloride at the less hindered aziridine carbon atom toward 2-chloromethyl-4-phenylpiperidine-4-carbonitriles **9** and **11**.

Alternatively, *trans*-piperidines **11** were isolated more easily performing the 6-*exo*-*tet* ring-expansion reaction on the diastereomeric mixture of aziridines **6** and **7**, as *trans*-piperidines **11** could be crystallized from the reaction mixture using ethanol as a solvent [40−43% of piperidines **11** starting from 2-(2-cyano-2-phenylethyl)aziridines, **5**]. The relative stereochemistry of *trans*-2-chloromethyl-4-phenylpiperidine-4-carbonitriles, **11**, was unambiguously assigned by X-ray crystallographic analysis of piperidine **11b** (see Supporting Information).

2-Chloromethyl-4-phenylpiperidine-4-carbonitriles **9** and **11** exhibit a number of interesting structural characteristics, making them suitable substrates for further elaboration. For example, the presence of a cyano substituent at the 4-position of the piperidine backbone provides an entry into conformationally restricted amino acid derivatives. Additionally, the 2-chloromethyl moiety is susceptible to nucleophilic substitution reactions, both intra- and intermolecularly.

β- and γ-Amino acids are known to possess unique pharmacological properties, and their applications as building blocks for the corresponding β- and γ-peptides make these compounds of high relevance in synthetic and medicinal chemistry.[18] Besides their use in peptidomimetics, some β-amino acids exhibit strong antibacterial activity (e.g., cispentacin),[18b] while γ-amino acids are used for the treatment of epilepsy, Parkinson disease, and schizophrenia (e.g., GABA analogues).[19] In continuation of our interest in β-amino acid chemistry,[20] intensive efforts were devoted to the development of new entries toward different constrained amino acids bearing a piperidine moiety in their structure, starting from the corresponding nitriles. Due to the synthetic utility of nitriles as precursors of carboxylic acids, esters, and amides, the search for novel types of functionalized aminonitriles has become an important challenge in organic synthesis.[21]

In the first part of this work, *cis*-piperidine **9c** was hydrolyzed, utilizing a HCl (3 M)/HOAc (6 M) mixture in water under microwave irradiation for 1 h at 150 °C, resulting in the formation of an inseparable mixture of 2-(chloromethyl)- and 2-(hydroxymethyl)piperidines **12** and **13** (ratio 2:3). Subsequently, this mixture was treated with 2 equiv of LiOH in water for 30 min under reflux, followed by purification on Dowex (H^+, 50 × 8−100), furnishing ammonium *cis*-1-(4-chlorobenzyl)-2-hydroxymethyl-4-phenylpiperidine-4-carboxylate, **14**, as the sole reaction product in 80% yield (Scheme 3).

Furthermore, *trans*-piperidine **11c** was subjected to reaction conditions similar to those of *cis*-isomer **9c**, i.e. hydrolysis

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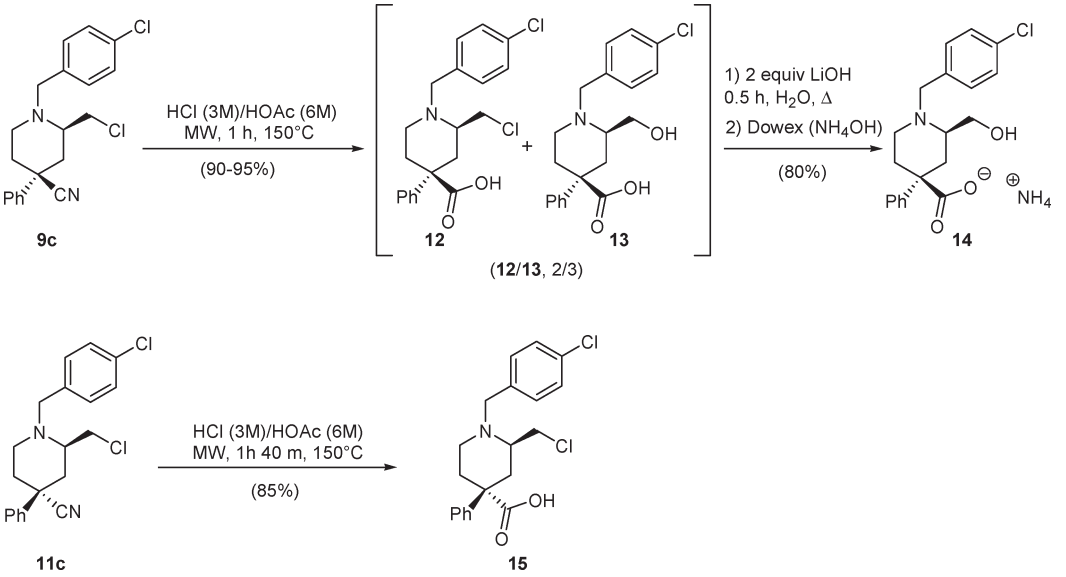
SCHEME 3



using a HCl (3 M)/HOAc (6 M) mixture in water under microwave irradiation for 1 h 40 min at 150 °C, furnishing *trans*-1-(4-chlorobenzyl)-2-chloromethyl-4-phenylpiperidine-4-carboxylic acid **15** in 85% yield. Remarkably, no formation of the corresponding 2-(hydroxymethyl)piperidine was observed in the latter case, pointing to a considerable steric hindrance with regard to attack of the chlorinated carbon atom in piperidine **11c** and **15**. Stereodefined 4-phenylpiperidine-4-carboxylic acids **14** and **15** represent a new class of constrained γ-amino acids with biological relevance.

In light of the known biological importance of 3-aminoadipic acids,[22] efforts were made for the preparation of novel conformational constrained analogues bearing a piperidine framework. Thus, *cis*-2-chloromethyl-4-phenylpiperidine-4-carbonitrile **9c** was treated with 2 equiv of potassium cyanide in DMSO, furnishing the corresponding *cis*-2-cyanomethyl-4-phenylpiperidine-4-carbonitrile **16** after 1 h at 120 °C in 92% yield. From a mechanistic viewpoint, piperidine **9c** probably undergoes an intramolecular substitution reaction toward bicyclic aziridinium intermediate **8c**, followed by regiospecific ring opening of this aziridinium salt by cyanide at the least hindered position, although direct S_N2-substitution at the chlorinated atom cannot be excluded. Upon 3D-analysis of intermediate **8c**, the occurrence of a favorable $\pi-\pi$-stacking[23] between both aromatic rings can be observed, which results in steric hindrance at the substituted aziridinium carbon atom. This effect might (partially) explain the exclusive attack that occurred at the unhindered position, resulting in the selective formation of piperidine **16**. Next, both cyano groups in compound **16** were transformed to the corresponding carboxylic acids by acid hydrolysis. Thus, treatment of dicyanopiperidine **16** with a HCl (3 M)/HOAc (6 M) mixture in water gave rise to *cis*-2-carboxymethyl-1-(4-chlorobenzyl)-4-phenylpiperidine-4-carboxylic acid **17** in 95% yield as a new constrained analogue of 3-aminoadipic acid after reflux for 3 days (Scheme 4).

Analogously, *trans*-1-(4-chlorobenzyl)-2-chloromethyl-4-phenylpiperidine-4-carbonitrile **11c** was treated with 2 equiv of potassium cyanide in DMSO, resulting in a mixture of azepane-3,5-dicarbonitrile **18** and 2-(cyanomethyl)piperidine-4-carbonitrile **19** (ratio 3:10) after 1 h at 120 °C. Probably, due to the absence of $\pi-\pi$-stacking interaction, competition between attack at the unsubstituted and the substituted positions in aziridinium intermediate **10c** occurred, resulting in a mixture of azepane **18** and piperidine **19**. Interestingly, azepane **18** could be easily transformed into the thermodynamically more stable piperidine **19** by heating the mixture of azepane **18** and piperidine **19** in DMSO at 120 °C for 4 h, affording 2-(cyanomethyl)piperidine **19** as the sole reaction product. Eventually, a nitrile to acid functional group transformation was performed in acidic medium (HCl (3 M)/HOAc (6 M) in H_2O under reflux for 6 days), furnishing *trans*-2-carboxymethyl-1-(4-chlorobenzyl)-4-phenylpiperidine-4-carboxylic acid **20** in 95% yield (Scheme 4). In summary, the above-described methodology allows the stereoselective preparation of both diastereomers of 2-carboxymethyl-4-phenylpiperidine-4-carboxylic acids **17** and **20** as biologically relevant targets, underlining to the synthetic utility of this approach.

In addition to cyanide, acetate was used as an oxygen nucleophile for the synthesis of versatile β-amino alcohols using the same approach as described above. β-Amino alcohols comprise an important class of compounds, as this moiety is found in a wide variety of biologically active alkaloids and peptides.[24] Furthermore, β-amino alcohols find applications as building blocks in the synthesis of various natural products and pharmaceuticals,[25] and they

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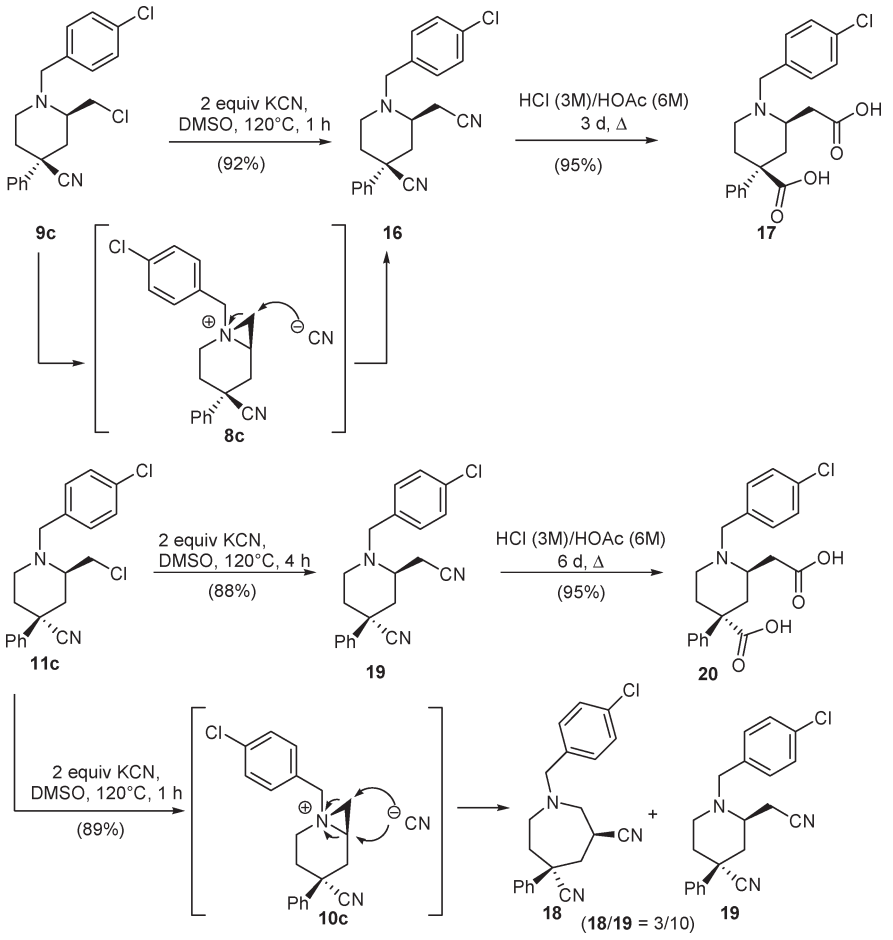
SCHEME 4



are useful as chiral auxiliaries for asymmetric synthesis and catalysis.[26]

cis-2-Chloromethyl-4-phenylpiperidine-4-carbonitriles **9a**,**c** were treated with 2 equiv of sodium acetate in ethanol, affording *cis*-6-acetoxy-4-phenylazepane-4-carbonitriles **21** and *cis*-2-acetoxymethyl-4-phenylpiperidine-4-carbonitriles **22** in a ratio of 1:2 after 2 h under reflux (Scheme 5). Again, the reaction proceeded *via* intermediate bicyclic aziridinium salts **8a**,**c**, followed by preferential ring opening of the latter salts by acetate at the least hindered position. In this case, prolonged heating did not afford a single thermodynamic product, in contrast with the synthesis of aminonitriles **19** (Scheme 4). Furthermore, changing the solvent from ethanol to DMSO did not alter the isomeric ratio of the obtained products **21** and **22**. Unfortunately, piperidines **22** and azepanes **21** appeared to be inseparable by column chromatography on silica gel.

Finally, acetates **21b** and **22b** were hydrolyzed using 2 equiv of lithium hydroxide in methanol under reflux for 2 h, furnishing a mixture of *cis*-6-hydroxy-4-phenylazepane-4-carbonitrile **23** and *cis*-2-hydroxymethyl-4-phenylpiperidine-4-carbonitrile **24** in 83% yield (Scheme 5). Piperidine **24** was separated through column chromatography on silica gel, providing a pure sample suitable for full spectroscopic characterization.

Analogously, *trans*-piperidine **11c** was subjected to a nucleophilic substitution reaction using sodium acetate in ethanol. In this case, the reaction proceeded more sluggishly, and only after 13 h of reflux was the substrate consumed completely, affording a mixture of *trans*-6-acetoxy-4-phenylazepane-4-carbonitrile **25** and *trans*-2-acetoxymethyl-4-phenylpiperidine-4-carbonitrile **26** (**25**/**26**, 3:1). Due to the long reaction time, partial formation (26%) of hydrolyzed products **27** and **28** was observed as well under the given reaction conditions, making a full characterization of acetates **25** and **26** impossible. In an attempt to shorten the reaction time, experiments were conducted using microwave irradiation, resulting in a reduction of the conversion time from 13 h to 20 min at 110 °C using 2 equiv of NaOAc in EtOH. Also in this case, the reaction mixture contained a mixture of both the acetates **25** and **26** as major components (74%) and alcohols **27** and **28** as minor impurities (26%).

Again, functional group transformation of the acetate to corresponding alcohol was performed using 2 equiv of LiOH in MeOH for 1 h at reflux temperature, furnishing *trans*-6-hydroxy-4-phenylazepane-4-carbonitrile **27** and *trans*-2-hydroxymethyl-4-phenylpiperidine-4-carbonitrile **28** in 79% yield in a ratio of 3:1 (**27**/**28**). Carbonitrile **27** was separated *via* column chromatography on silica gel, affording an analytically pure sample.

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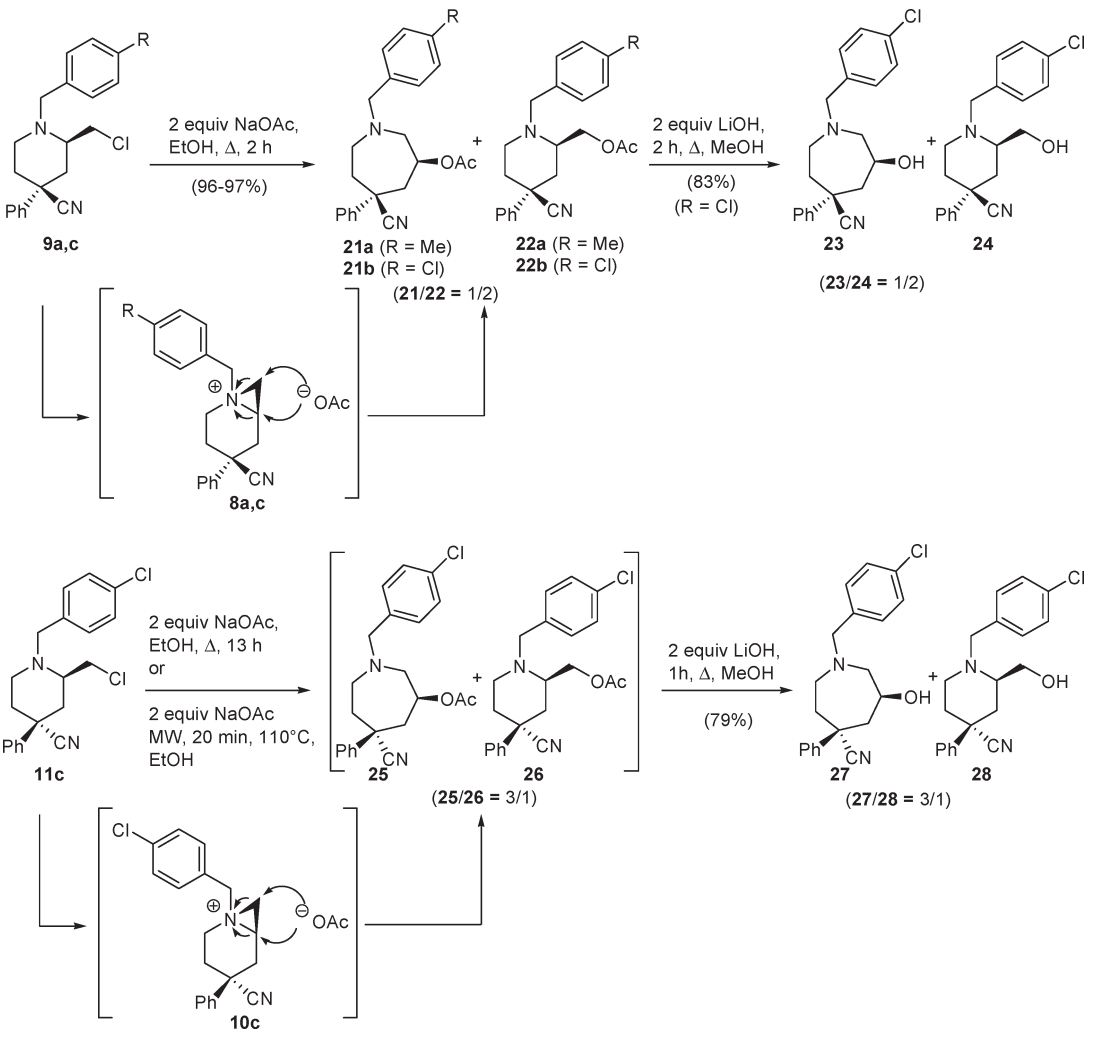
SCHEME 5



It should be remarked that, starting from *cis*-piperidines **9a**,**c**, the preferential formation of piperidines **22** was observed, whereas azepane **25** was the major reaction product if *trans*-piperidine **11c** was used as a substrate. This observation can partially be explained by considering $\pi-\pi$-stacking in intermediates **8a**,**c**, making an attack at the substituted aziridinium carbon atom more difficult due to steric hindrance. In addition, the polarizability of the nucleophiles might play an important role with regard to the regioselectivity, with cyanide being a strong and acetate a moderate nucleophile.

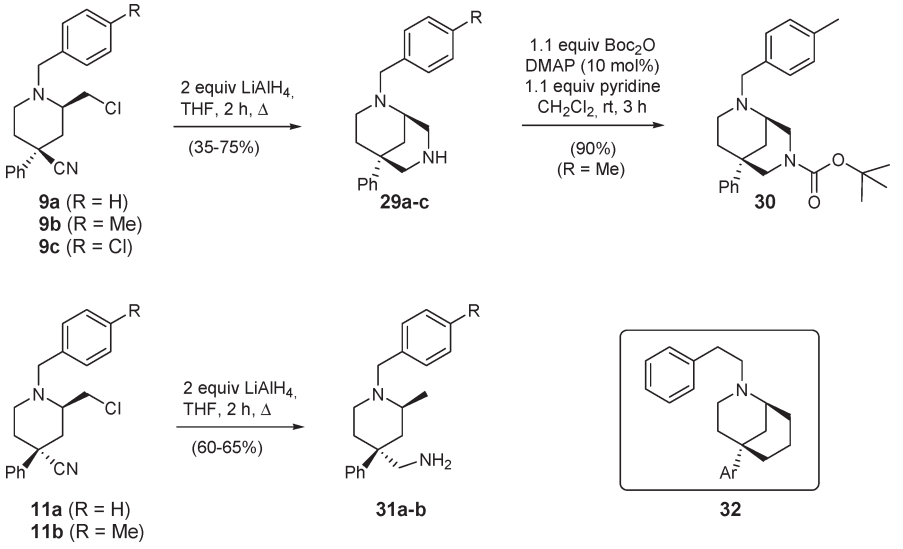
It should be noted that the ring enlargement of 2-(halomethyl)piperidines to 3-substituted azepanes *via* intermediate aziridinium salts has only been described sporadically in the literature.[27]

Finally, attempts were made to induce dehydrochlorination of 2-chloromethyl-4-phenylpiperidine-4-carbonitriles **9** and **11**, followed by migration of the double bond toward the thermodynamically more stable endocyclic position in order to form tetrahydropyridine-4-carbonitriles. Many bases (KO*t*Bu, NaH, LDA) and solvents (THF, *t*BuOH, DMSO) were used, but complex reaction mixtures were obtained in all cases.

Next to intermolecular nucleophilic substitutions with cyanide and acetate, an intramolecular reaction of *cis*-2-(chloromethyl)piperidines **9** was examined, taking advantage of the presence of a nitrile group at the 4-position as a masked aminomethyl moiety. Gratifyingly, treatment of piperidines **9** with 2 equiv of $LiAlH_4$ in THF afforded 5-phenyl-2,7-diazabicyclo[3.3.1]nonanes **29** as single reaction products (Scheme 6, yields after purification). This conversion proceeded *via* the formation of an aminomethyl substituent through cyanide reduction, which subsequently induced an intramolecular 6-*exo*-*tet* ring closure toward 5-phenyl-2,7-diazabicyclo[3.3.1]nonanes **29** by attack of the free amino moiety onto the chlorinated carbon atom. At first sight, it cannot be excluded that this ring-closing reaction proceeds *via* an intermediate bicyclic aziridinium salt **8** as described above, which might give rise to 6-phenyl-3,8-diazabicyclo[4.2.1]nonanes upon ring opening as an alternative for 5-phenyl-2,7-diazabicyclo[3.3.1]nonanes **29**. In order to confirm the presence of a bicyclo[3.3.1]nonane instead of a bicyclo[4.2.1]nonane skeleton in the obtained

(27) (a) Chong, H.-S.; Garmestani, K.; Bryant, H. L., Jr.; Brechbiel, M. W. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2080. (b) Chong, H.-S.; Garmestani, K.; Bryant, H. L., Jr.; Brechbiel, M. W. *J. Org. Chem.* **2001**, *66*, 7745. (c) Berkes, D.; Decroix, B. *B. Soc. Chim. Fr.* **1994**, *131*, 986. (d) Morie, T.; Kato, S.; Harada, H.; Fujiwara, I.; Watanabe, K.; Matsumoto, J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2565.

SCHEME 6



reaction products, the free amino group at the 7-position was protected with a *tert*-butoxycarbonyl group using 1.1 equiv of di-*tert*-butyl dicarbonate, 1.1 equiv of pyridine, and DMAP (10 mol %) as the catalyst in CH_2Cl_2 for 3 h at room temperature (Scheme 6). This protection step resulted in substantial shifts of the signals of two CH_2N carbon atoms in the Boc-protected amine **30** (46.39 ppm → 42.84 ppm and 58.68 ppm → 53.19 ppm, ^{13}C NMR, $CDCl_3$), whereas a less pronounced shift was observed for the CHN signal (52.09 ppm → 50.82 ppm). These observations point into the direction of a bicyclo[3.3.1]nonane backbone. In order to resolve all doubts, X-ray analysis of compound **29c** unambiguously assigned the 5-phenyl-2,7-diazabicyclo[3.3.1]nonane system present in compounds **29** obtained through reduction of piperidines **9** by $LiAlH_4$ (see Supporting Information).

In this way, a convenient entry toward the 2,7-diazabicyclo-[3.3.1]nonane[28] skeleton is presented through a straightforward approach. These compounds **29** can be regarded as novel aza-analogues of 5-phenylmorphans **32**, which act as opioid agonists or antagonists.[29]

In analogy, *trans*-piperidines **11a**,**b** were treated with 2 equiv of $LiAlH_4$ in THF under refux for 2 h, resulting in the formation of *trans*-4-aminomethyl-2-methyl-4-phenylpiperidines **31** in 60−65% yield (Scheme 6). The dechlorination of 2-(chloromethyl)piperidines **11** can take place *via* initial formation of an intermediate aziridinium salt **10** or *via* direct dechlorination, following either an ionic or a radical pathway.[30] 4-(Aminomethyl)piperidines have been patented as potent tachykinin antagonists for the treatment of pain and inflammation,[4] and can be used for the treatment of epilepsy, anxiety and inflammatory diseases.[31]

In conclusion, a short and convenient approach toward novel *cis*- and *trans*-2-chloromethyl-4-phenylpiperidine-4-carbonitriles is reported starting from 2-(2-cyano-2-phenylethyl)-aziridines. Furthermore, the high synthetic flexibility of these piperidine building blocks was demonstrated by the synthesis of a variety of stereodefined conformationally constrained amino acids, *β*-amino alcohols, and unprecedented 2,7-diazabicyclo-[3.3.1]nonanes.

Experimental Section

General. ^1H NMR spectra were recorded at 300 MHz (JEOL ECLIPSE+) with tetramethylsilane as internal standard. ^{13}C NMR spectra were recorded at 75 MHz (JEOL ECLIPSE+). Mass spectra were recorded on an Agilent 1100 series mass spectrometer using either a direct inlet system (electron spray, 4000 V) or LC−MS coupling (UV detector). IR spectra were recorded on a Perkin-Elemer Spectrum BX FT-IR spectrometer. All compounds were analysed in neat form with an attenuated total reflectance (ATR) accessory. Melting points were measured using a Büchi B-540 apparatus and are uncorrected. Dichloromethane was distilled over calcium hydride, while diethyl ether and THF were distilled from sodium and sodium benzophenone ketyl before use. Microwave reactions were performed in a CEM Discover Microwave Reactor (200 W_{max}) in an 80-mL sealed vessel using a fiber-optic temperature sensor.

Synthesis of 4-Chloro-2-[1-(arylmethyl)aziridin-2-ylmethyl]-2-phenylbutyronitriles, 6 and 7. As a representative example, the synthesis of 4-chloro-2-[1-benzylaziridin-2-ylmethyl]-5-phenylbutyronitriles **6a** and **7a** is described here. To an ice-cooled solution of diisopropylamine (60 mmol, 1.2 equiv) in dry THF (75 mL) was added *n*-BuLi (1.2 equiv, 2.5 M) *via* a syringe under nitrogen atmosphere, and the resulting solution was stirred for 15 min at 0 °C. Subsequently, a solution of 1-benzyl-2-(2-cyano-2-phenylethyl)aziridine **5a** (50 mmol)[12b] in THF (20 mL) was added *via* a syringe at 0 °C, and the resulting solution was stirred for 1 h at 0 °C. Finally, 1-bromo-2-chloroethane (55 mmol, 1.1 equiv) was added *via* a syringe at 0 °C, and the reaction mixture was stirred for 1 h at 0 °C under nitrogen atmosphere. The reaction mixture was poured into a saturated NH_4Cl solution

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(75 mL) and was extracted with Et_2O (3 × 75 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent in vacuo afforded 4-chloro-2-[1-benzylaziridine-2-ylmethyl]-2-phenylbutyronitriles **6a** and **7a** as a mixture of isomers (~1:1). Isolation of the mixture of (2*R*,2′*R*)- and (2*S*,2′*S*)-isomers **6a** was realized by means of a selective crystallization from ethanol, whereas the (2*R*,2′*S*)- and (2*S*,2′*R*)-isomers **7a** were obtained by column chromatography on silica gel (hexane/EtOAc, 3:1).

(2*R*,2′*R*)- and (2*S*,2′*S*)-2-[1-Benzylaziridin-2-ylmethyl]-4-chloro-2-phenylbutyronitrile, 6a: (38%) white crystals. Mp = 79.7 °C. R_f = 0.21 (hexane/EtOAc, 3:1). ^{1}H NMR ($CDCl_3$) δ 1.39−1.47 (2H, m); 1.75 (1H, d, J = 2.8 Hz); 2.03 and 2.26 (2H, 2 × dd, J = 14.0, 5.8, 5.2 Hz); 2.38 (1H, ddd, J = 13.7, 11.3, 5.1 Hz); 2.52 (1H, ddd, J = 13.7, 11.1, 5.4 Hz); 2.92 and 3.23 (2H, 2 × d, J = 12.9 Hz); 3.19 (1H, ddd, J = 11.0, 10.9, 4.8 Hz); 3.56 (1H, ddd, J = 11.1, 11.0, 5.3 Hz); 7.13−7.52 (10H, m). ^{13}C NMR ($CDCl_3$) δ 33.8 (CH_2); 35.2 (CH); 39.4 (CH_2); 43.2 (CH_2); 44.2 (CH_2); 46.1 (C); 64.3 (CH_2); 121.4 (C); 126.1 (CH); 127.3 (CH); 128.3 (CH); 128.5 (CH); 128.6 (CH); 129.4 (CH); 136.4 (C); 138.7 (C). IR (cm^{-1}): ν_{CN} = 2236. MS (70 eV): m/z (%): 325/7 (M^+ + 1, 100). Anal. Calcd for $C_{20}H_{21}ClN_2$: C 73.95; H 6.52; N 8.62. Found: C 74.23; H 6.87; N 8.49.

(2*S*, 2′*R*)- and (2*R*, 2′*S*)-2-[1-Benzylaziridin-2-ylmethyl]-4-chloro-2-phenylbutyronitrile 7a: (15%) yellow oil. R_f = 0.13 (hexane/EtOAc, 3:1). ^{1}H NMR ($CDCl_3$) δ 1.32 (1H, d, J = 6.1 Hz); 1.40 (1H, d, J = 3.9 Hz); 1.63−1.70 (1H, m); 2.02 and 2.10 (2H, 2 × dd, J = 14.3, 7.2, 5.5 Hz); 2.34 (1H, ddd, J = 13.8, 11.3, 5.1 Hz); 2.48 (1H, ddd, J = 13.8, 11.0, 5.5 Hz); 3.14 (1H, ddd, J = 11.0, 11.0, 5.0 Hz); 3.46 (1H, ddd, J = 11.0, 11.0, 5.6 Hz); 3.19 and 3.64 (2H, 2 × d, J = 12.7 Hz); 7.23−7.47 (1H, m). ^{13}C NMR ($CDCl_3$) δ 33.3 (CH_2); 35.4 (CH); 39.4 (CH_2); 42.4 (CH_2); 44.7 (CH_2); 46.1 (C); 64.6 (CH_2); 121.1 (C); 125.8 (CH); 127.5 (CH); 128.5 (CH); 128.6 (CH); 128.6 (CH); 129.3 (CH); 137.1 (C); 138.5 (C). IR (cm^{-1}): ν_{CN} = 2237. MS (70 eV): m/z (%): 325/7 (M^+ + 1, 100). Anal. Calcd for $C_{20}H_{21}ClN_2$: C 73.95; H 6.52; N 8.62. Found: C 74.20; H 6.72; N 8.51.

Synthesis of *cis*-1-Arylmethyl-2-chloromethyl-4-phenylpiperidine-4-carbonitriles, 9. As a representative example, the synthesis of *cis*-1-benzyl-2-chloromethyl-4-phenylpiperidine-4-carbonitrile **9a** is described here. A solution of 2-[1-benzylaziridin-2-ylmethyl]-4-chloro-2-phenylbutyronitrile **6a** (20 mmol) in acetonitrile (20 mL) was placed in an 80-mL sealed glass vessel, provided with an appropriate stirring bar and subjected to microwave conditions (136 °C, 30 min). Afterward, evaporation of the solvent afforded *cis*-1-benzyl-2-chloromethyl-4-phenylpiperidine-4-carbonitrile **9a** in quantitative yield.

***cis*-1-Benzyl-2-chloromethyl-4-phenylpiperidine-4-carbonitrile, 9a:** (99%) yellow oil. R_f = 0.15 (hexane/EtOAc, 3:1). ^{1}H NMR ($CDCl_3$) δ 2.11−2.35 (3H, m); 2.56−2.66 (2H, m); 2.98 (1H, ddd, J = 12.8, 9.5, 3.2 Hz); 3.16 (1H, m); 3.66 and 3.87 (2H, 2 × d, J = 13.5 Hz); 3.87 and 4.19 (2H, 2 × dd, J = 11.3, 9.1, 4.7 Hz); 7.23−7.52 (10H, m). ^{13}C NMR ($CDCl_3$) δ 35.0 (CH_2); 36.1 (CH_2); 38.5 (C); 42.3 (CH_2); 44.2 (CH_2); 58.4 (CH_2); 58.5 (CH); 124.0 (C); 126.2 (CH); 127.5 (CH); 128.3 (CH); 128.6 (CH); 129.3 (CH); 138.6 (C); 139.4 (C). IR (cm^{-1}): ν_{CN} = 2231. MS (70 eV): m/z (%): 325/7 (M^+ + 1, 100). Anal. Calcd for $C_{20}H_{21}ClN_2$: C 73.95; H 6.52; N 8.62. Found: C 74.31; H 6.74; N 8.49.

Synthesis of *trans*-1-Arylmethyl-2-chloromethyl-4-phenylpiperidine-4-carbonitriles, 11. As a representative example, the synthesis of *trans*-1-benzyl-2-chloromethyl-4-phenylpiperidine-4-carbonitrile **11a** is described here. A solution of 2-[1-benzylaziridin-2-ylmethyl]-4-chloro-2-phenylbutyronitrile **7a** (17.5 mmol) in acetonitrile (20 mL) was placed in an 80-mL sealed glass vessel, provided with an appropriate stirring bar and subjected to microwave conditions (136 °C, 30 min). Afterward, evaporation of the solvent afforded *trans*-1-benzyl-2-chloromethyl-4-phenylpiperidine-4-carbonitrile **11a** in a quantitative yield.

***trans*-1-Benzyl-2-chloromethyl-4-phenylpiperidine-4-carbonitriles, 11a:** (99%) white crystals. Mp = 115.1 °C. R_f = 0.21 (hexane/EtOAc, 3:1). ^{1}H NMR ($CDCl_3$) δ 1.98−2.02 (2H, m); 2.14−2.28 (2H, m); 2.57 (1H, ddd, J = 12.5, 8.4, 6.2 Hz); 2.95−3.05 (2H, m); 3.18 (1H, d, J = 13.2 Hz); 3.63 and 3.96 (2H, 2 × dd, J = 12.1, 5.0, 1.7 Hz); 4.21 (1H, d, J = 13.2 Hz); 7.23−7.51 (10H, m). ^{13}C NMR ($CDCl_3$) δ 35.9 (CH_2); 40.9 (CH_2); 43.3 (C); 46.6 (CH_2); 49.3 (CH_2); 57.3 (CH_2); 59.1 (CH); 122.2 (C); 125.7 (CH); 127.4 (CH); 128.4 (CH); 128.6 (CH); 129.2 (CH); 138.4 (C); 139.9 (C). IR (cm^{-1}): ν_{CN} = 2233. MS (70 eV): m/z (%): 325/7 (M^+ + 1, 100). Anal. Calcd for $C_{20}H_{21}ClN_2$: C 73.95; H 6.52; N 8.62. Found: C 74.11; H 6.68; N 8.66.

Synthesis of Ammonium *cis*-1-(4-Chlorobenzyl)-2-hydroxymethyl-4-phenylpiperidine-4-carboxylate, 14. To a solution of *cis*-1-(4-chlorobenzyl)-2-chloromethyl-4-phenylpiperidine-4-carbonitrile (1.4 mmol) **9c** in water (5 mL) was added 3 M hydrochloric acid (1.62 mL) and 6 M acetic acid (3.42 mL). The mixture was placed in an 80-mL sealed glass vessel, provided with an appropriate stirring bar and subjected to microwave conditions (150 °C, 1 h). Afterward, the solvent was evaporated under high vacuum, and the residue was redissolved in water (10 mL). Subsequently, LiOH (2.4 mmol, 2 equiv) was added to this solution, after which the resulting mixture was heated under reflux for 30 min. Isolation of ammonium *cis*-1-(4-chlorobenzyl)-2-hydroxymethyl-4-phenylpiperidine-4-carboxylate **14** was realized by means of ion-exchange chromatography on Dowex H^+ (50 × 8−100).

Ammonium *cis*-1-(4-Chlorobenzyl)-2-hydroxymethyl-4-phenylpiperidine-4-carboxylate, 14: (80%) white crystals. Mp = 228.3 °C. ^{1}H NMR (CD_3OD) δ 2.14 (1H, ddd, J = 14.9, 11.6, 3.6 Hz); 2.26 (1H, dd, J = 14.9, 11.0 Hz); 2.45 (1H, dt, J = 12.2, 2.4 Hz); 2.58 (1H, d (broad), J = 14.9 Hz); 2.74 (1H, d (broad), J = 14.9 Hz); 2.83−2.86 (1H, m); 2.95 (1H, dt, J = 12.2, 3.6 Hz); 3.57 (1H, d, J = 13.2 Hz); 3.78 and 3.93 (2H, 2 × dd, J = 12.1, 5.0, 3.9 Hz); 4.36 (1H, d, J = 13.2 Hz); 7.16−7.50 (9H, m). ^{13}C NMR (CD_3OD) δ 30.6 (CH_2); 34.3 (CH_2); 41.1 (C); 48.5 (CH_2); 55.6 (CH_2); 60.8 (CH); 61.3 (CH_2); 126.0 (CH); 127.0 (CH); 128.2 (CH); 128.4 (CH); 131.8 (CH); 126.8 (C); 134.2 (C); 141.5 (C); 180.5 (C). IR (cm^{-1}): ν_{OH} = 3365, ν_{CO} = 1579. MS (70 eV): m/z (%): 360/2 (M^+ + 1, 100). Anal. Calcd for $C_{20}H_{25}ClN_2O_3$: C 63.74; H 6.69; N 7.43. Found: C 63.86; H 6.81; N 7.23.

Synthesis of *trans*-1-(4-Chlorobenzyl)-2-chloromethyl-4-phenylpiperidine-4-carboxylic Acid, 15. To a solution of *trans*-1-(4-chlorobenzyl)-2-chloromethyl-4-phenylpiperidine-4-carbonitrile (1.4 mmol) **11c** in water (5 mL) was added 3 M hydrochloric acid (1.62 mL) and 6 M acetic acid (3.42 mL). The mixture was placed in an 80-mL sealed glass vessel, provided with an appropriate stirring bar and subjected to microwave conditions (150 °C, 1 h 40 min). Afterward, the solvent was evaporated under high vacuum, affording *trans*-1-(4-chlorobenzyl)-2-chloromethyl-4-phenylpiperidine-4-carboxylic acid **15** in good yield and high purity (> 95% based on NMR analysis).

***trans*-1-(4-Chlorobenzyl)-2-chloromethyl-4-phenylpiperidine-4-carboxylic acid, 15:** (85%) white crystals. Mp = 216.6 °C. ^{1}H NMR (CD_3OD) δ 1.92−2.03 (1H, m); 2.20 (1H, dd, J = 14.5, 12.4 Hz); 2.73 (1H, d (broad), J = 14.3 Hz); 2.89 (1H, dd, J = 14.5, 2.5 Hz,); 3.10 (1H, dt, J = 13.3, 2.5 Hz); 3.34 (1H, ddd, J = 13.3, 4.0, 2.6 Hz); 3.81−3.86 (1H, m); 4.05 (1H, dd, J = 13.4, 2.5 Hz); 4.13 (1H, d, J = 13.2 Hz); 4.38−4.42 (1H, m); 4.70 (1H, d, J = 13.2 Hz); 7.18−7.48 (9H, m). ^{13}C NMR (CD_3OD) δ 30.0 (CH_2); 35.2 (CH_2); 42.8 (CH_2); 48.2 (C); 49.8 (CH_2); 55.2 (CH_2); 62.3 (CH); 125.1 (CH); 127.7 (CH); 128.7 (CH); 129.3 (CH); 133.2 (CH); 127.4 (C); 136.3 (C); 141.0 (C); 174.4 (C). IR (cm^{-1}): ν_{OH} = 3362, ν_{CO} = 1715. MS (70 eV): m/z (%): 378/80/82 (M^+ + 1, 100). Anal. Calcd for $C_{20}H_{21}Cl_2NO_2$: C 63.50; H 5.60; N 3.70. Found: C 63.77; H 5.95; N 3.51.

Synthesis of *cis*-1-(4-Chlorobenzyl)-2-cyanomethyl-4-phenylpiperidine-4-carbonitrile, 16. To a solution of *cis*-1-(4-chlorobenzyl)-2-chloromethyl-4-phenylpiperidine-4-carbonitrile (1.0 mmol) **9c** in

DMSO (10 mL) was added potassium cyanide (2 mmol, 2 equiv), and the resulting solution was heated for 1 h at 120 °C. The reaction mixture was poured into water (10 mL) and extracted with Et_2O (3 × 10 mL). Drying ($MgSO_4$), filtration of the drying agent, and evaporation of the solvent in vacuo afforded *cis*-1-(4-chlorobenzyl)-2-cyanomethyl-4-phenylpiperidine-4-carbonitrile **16**, which was isolated in pure form by means of column chromatography on silica gel (hexane/EtOAc, 3:1).

***cis*-1-(4-Chlorobenzyl)-2-cyanomethyl-4-phenylpiperidine-4-carbonitrile, 16:** (92%) white crystals. Mp = 135.3 °C. R_f = 0.16 (hexane/EtOAc, 3:1). ^{1}H NMR ($CDCl_3$) δ 2.08−2.25 (2H, m); 2.35 and 2.45 (2H, 2 × dd, J = 14.4, 5.0, 3.6 Hz); 2.55−2.62 (1H, m); 2.80 (1H, dd, J = 17.1, 5.5 Hz); 2.82−2.90 (1H, m); 3.09 (1H, dd, J = 17.1, 8.3 Hz); 3.29−3.37 (1H, m); 3.55 and 3.72 (2H, 2 × d, J = 13.2 Hz); 7.22−7.48 (9H, m). ^{13}C NMR ($CDCl_3$) δ 16.9 (CH_2); 34.9 (CH_2); 38.2 (CH_2); 38.4 (C); 43.5 (CH_2); 54.1 (CH); 57.6 (CH_2); 118.6 (C); 123.9 (C); 126.1 (CH); 128.6 (CH); 128.8 (CH); 129.4 (CH); 130.0 (CH); 132.2 (C); 136.6 (C); 138.9 (C). IR (cm^{-1}): ν_{CN} = 2249. MS (70 eV): m/z (%): 350/2 ($M^+ + 1$, 100). Anal. Calcd for $C_{21}H_{20}ClN_3$: C 72.09; H 5.76; N 12.01. Found: C 72.19; H 5.84; N 11.93.

Synthesis of *cis*-2-Carboxymethyl-1-(4-chlorobenzyl)-4-phenylpiperidine-4-carboxylic Acid, 17. To a solution of *cis*-1-(4-chlorobenzyl)-2-cyanomethyl-4-phenylpiperidine-4-carbonitrile **16** (0.43 mmol) in water (5 mL) was added 3 M hydrochloric acid (1.62 mL) and 6 M acetic acid (3.42 mL) at room temperature, and the resulting solution was heated under reflux for 3 days. Isolation of *cis*-2-carboxymethyl-1-(4-chlorobenzyl)-4-phenylpiperidine-4-carboxylic acid **17** was performed by crystallization from the resulting solution upon standing at room temperature for 2 days.

***cis*-2-Carboxymethyl-1-(4-chlorobenzyl)-4-phenylpiperidine-4-carboxylic acid, 17:** (95%) white crystals. Mp = 169.5 °C. ^{1}H NMR (CD_3OD) δ 2.26−2.37 (1H, m); 2.39 (1H, dd, J = 15.4, 11.6 Hz); 2.78−2.90 (2H, m); 3.04 (1H, dd, J = 17.3, 7.4 Hz); 3.14 (1H, d, J = 15.4 Hz); 3.24−3.31 (2H, m); 3.56−3.63 (1H, m); 3.98 and 4.72 (2H, 2 × d, J = 13.2 Hz); 7.32−7.58 (9H, m). ^{13}C NMR (CD_3OD) δ 29.1 (CH_2); 34.7 (CH_2); 35.0 (CH_2); 46.8 (C); 48.4 (CH_2); 55.8 (CH_2); 58.0 (CH); 127.1 (CH); 127.7 (CH); 127.7 (CH); 129.1 (CH); 132.9 (CH); 136.0 (C); 136.8 (C); 171.8 (C); 175.1 (C). IR (cm^{-1}): ν_{OH} = 3010 ν_{CO} = 1724. MS (70 eV): m/z (%): 388/90 ($M^+ + 1$, 100). Anal. Calcd for $C_{21}H_{22}ClNO_4$: C 65.03; H 5.72; N 3.61. Found: C 65.46; H 5.92; N 3.48.

Synthesis of *trans*-1-(4-Chlorobenzyl)-5-phenylazepane-3,5-dicarbonitrile, 18. To a solution of *trans*-1-(4-chlorobenzyl)-2-chloromethyl-4-phenylpiperidine-4-carbonitrile **11c** (0.5 mmol) in DMSO (10 mL) was added potassium cyanide (1 mmol, 2 equiv), and the resulting solution was heated at 120 °C for 1 h. The reaction mixture was poured into water (10 mL) and extracted with Et_2O (3 × 10 mL). Drying ($MgSO_4$), filtration of the drying agent, and evaporation of the solvent in vacuo afforded a mixture of *trans*-1-(4-chlorobenzyl)-5-phenylazepane-3,5-dicarbonitrile **18** and *trans*-1-(4-chlorobenzyl)-2-cyanomethyl-4-phenylpiperidine-4-carbonitrile **19** in a 3:10 ratio (**18**/**19**). *trans*-1-(4-Chlorobenzyl)-5-phenylazepane-3,5-dicarbonitrile **18** was isolated in pure form by means of column chromatography on silica gel (hexane/EtOAc, 3:1).

***trans*-1-(4-Chlorobenzyl)-5-phenylazepane-3,5-dicarbonitrile, 18:** (21%) yellow oil. R_f = 0.22 (hexane/EtOAc, 3:1). ^{1}H NMR ($CDCl_3$) δ 2.18−2.25 (2H, m); 2.45−2.51 (2H, m); 2.87−3.01 (2H, m); 3.03−3.24 (3H, m); 3.71 and 3.81 (2H, 2 × d, J = 13.2 Hz); 7.26−7.50 (9H, m). ^{13}C NMR ($CDCl_3$) δ 29.9 (CH); 40.7 (CH_2); 42.2 (CH_2); 44.9 (C); 51.8 (CH_2); 55.0 (CH_2); 62.0 (CH_2); 120.5 (C); 121.0 (C); 125.1 (CH); 128.5 (CH); 128.9 (CH); 129.4 (CH); 130.2 (CH); 133.4 (C); 136.8 (C); 141.2 (C). IR (cm^{-1}): ν_{CN} = 2238. MS (70 eV): m/z (%): 350/2 ($M^+ + 1$, 100). Anal. Calcd for $C_{21}H_{20}ClN_3$: C 72.09; H 5.76; N 12.01. Found: C 71.90; H 5.86; N 12.17.

Synthesis of *trans*-1-(4-Chlorobenzyl)-2-cyanomethyl-4-phenylpiperidine-4-carbonitrile, 19. To a solution of *trans*-1-(4-chlorobenzyl)-2-chloromethyl-4-phenylpiperidine-4-carbonitrile (1.0 mmol) **11c** in DMSO (10 mL) was added potassium cyanide (2 mmol, 2 equiv), and the resulting solution was heated for 5 h at 120 °C. The reaction mixture was poured into water (10 mL) and extracted with Et_2O (3 × 10 mL). Drying ($MgSO_4$), filtration of the drying agent, and evaporation of the solvent in vacuo afforded *trans*-1-(4-chlorobenzyl)-2-cyanomethyl-4-phenylpiperidine-4-carbonitrile **19**, which was isolated in pure form by means of column chromatography on silica gel (hexane/EtOAc, 3:1).

***trans*-1-(4-Chlorobenzyl)-2-cyanomethyl-4-phenylpiperidine-4-carbonitrile, 19:** (88%) white crystals. Mp = 129.9 °C. R_f = 0.16 (hexane/EtOAc, 3:1). ^{1}H NMR ($CDCl_3$) δ 2.03−2.08 (2H, m); 2.11−2.25 (2H, m); 2.50−2.59 (2H, m); 2.94−3.08 (3H, m); 3.18 and 4.12 (2H, 2 × d, J = 12.9 Hz); 7.26−7.52 (9H, m). ^{13}C NMR ($CDCl_3$) δ 23.3 (CH_2); 35.6 (CH_2); 42.7 (CH_2); 43.2 (C); 49.3 (CH_2); 55.0 (CH); 57.1 (CH_2); 116.7 (C); 121.7 (C); 125.6 (CH); 128.6 (CH); 128.8 (CH); 129.3 (CH); 130.3 (CH); 133.4 (C); 136.4 (C); 139.1 (C). IR (cm^{-1}): ν_{CN} = 2248. MS (70 eV): m/z (%): 350/2 ($M^+ + 1$, 100). Anal. Calcd for $C_{21}H_{20}ClN_3$: C 72.09; H 5.76; N 12.01. Found: C 72.21; H 5.93; N 11.92.

Synthesis of *trans*-2-Carboxymethyl-1-(4-chlorobenzyl)-4-phenylpiperidine-4-carboxylic Acid, 20. To a solution of *trans*-1-(4-chlorobenzyl)-2-cyanomethyl-4-phenylpiperidine-4-carbonitrile **19** (0,65 mmol) in water (5 mL) was added 3 M hydrochloric acid (1.62 mL) and 6 M acetic acid (3.42 mL) at room temperature, and the resulting solution was heated under reflux for 6 days. Isolation of *trans*-2-carboxymethyl-1-(4-chlorobenzyl)-4-phenylpiperidine-4-carboxylic acid **20** was performed by crystallization from the resulting solution upon standing at room temperature for 2 days.

***trans*-2-Carboxymethyl-1-(4-chlorobenzyl)-4-phenylpiperidine-4-carboxylic acid, 20:** (95%) white crystals. Mp = 243.3 °C. ^{1}H NMR (($CD_3)_2SO$) δ 1.88−2.02 (2H, m); 2.57 (1H, d, J = 13.0 Hz); 2.74−2.82 (2H, m); 2.92 (1H, t, J = 13.0 Hz); 3.12−3.25 (2H, m); 3.56−3.64 (1H, m); 4.11 and 4.53 (2H, 2 × d, J = 13.0 Hz); 7.24−7.53 (9H, m). ^{13}C NMR (($CD_3)_2SO$) δ 30.0 (CH_2N)) δ 36.9 (CH_2); 37.3 (CH_2); 48.3 (C); 49.3 (CH_2); 54.4 (CH_2); 58.8 (CH); 125.7 (CH); 128.2 (CH); 129.4 (CH); 129.5 (CH); 133.7 (CH); 135.0 (C); 141.9 (C); 171.8 (C); 174.6 (C). IR (cm^{-1}): ν_{OH} = 3240, ν_{CO} = 1742, 1692. MS (70 eV): m/z (%): 388/90 ($M^+ + 1$, 100). Anal. Calcd for $C_{21}H_{22}ClNO_4$: C 65.03; H 5.72; N 3.61. Found: C 65.41; H 5.94; N 3.39.

Synthesis of *cis*-6-Acetoxy-1-arylmethyl-4-phenylazepane-4-carbonitriles, 21, and *cis*-2-Acetoxymethyl-1-arylmethyl-4-phenylpiperidine-4-carbonitriles, 22. As a representative example, the synthesis of *cis*-6-acetoxy-1-(4-chlorobenzyl)-4-phenylazepane-4-carbonitrile **21b** and *cis*-2-acetoxymethyl-1-(4-chlorobenzyl)-4-phenylpiperidine-4-carbonitrile **22b** is presented here. To a solution of *cis*-1-(4-chlorobenzyl)-2-chloromethyl-4-phenylpiperidine-4-carbonitrile **9c** (0.95 mmol) in ethanol (10 mL) was added sodium acetate (1.9 mmol, 2 equiv), and the resulting solution was heated under reflux for 2 h. The reaction mixture was poured into water (10 mL) and extracted with Et_2O (3 × 10 mL). Drying ($MgSO_4$), filtration of the drying agent, and evaporation of the solvent in vacuo afforded *cis*-6-acetoxy-1-(4-chlorobenzyl)-4-phenylazepane-4-carbonitrile **21b** and *cis*-2-acetoxymethyl-1-(4-chlorobenzyl)-4-phenylpiperidine-4-carbonitrile **22b**. Isolation of pure samples of azepane **21b** and piperidine **22b** from the mixture by means of column chromatography on silica gel (hexane/EtOAc, 9:1) was not possible, and spectral data were derived from the mixture of **21b** and **22b**.

***cis*-6-Acetoxy-1-(4-chlorobenzyl)-4-phenylazepane-4-carbonitrile, 21b.** Spectral data were derived from a mixture of diastereomers. Yellow oil. R_f = 0.16 (hexane/EtOAc, 9:1). ^{1}H NMR ($CDCl_3$) δ 2.03 (3H, s); 2.17−2.28 (2H, m); 2.49−2.56 (2H, m);

2.81−3.14 (4H, m); 3.62 and 3.70 (2H, 2 × d, J = 13.8 Hz); 5.13−5.22 (1H, m); 7.21−7.54 (9H, m). ^{13}C NMR ($CDCl_3$) δ 21.3 (CH_3); 40.6 (CH_2); 42.3 (C); 43.4 (CH_2); 53.1 (CH_2); 57.5 (CH_2); 62.3 (CH_2); 70.4 (CH); 122.9 (C); 125.4 (CH); 128.0 (CH); 128.3 (CH); 130.3 (CH); 132.9 (C); 137.6 (C); 141.9 (C); 170.5 (C). IR (cm^{-1}): ν_{CO} = 1736 ν_{CN} = 2232. MS (70 eV): m/z (%): 383/5 (M^+ + 1, 100).

***cis*-2-Acetoxymethyl-1-(4-chlorobenzyl)-4-phenylpiperidine-4-carbonitrile, 22b.** Spectral data were derived from a mixture of diastereomers. Yellow oil. R_f = 0.16 (hexane/EtOAc, 9:1). ^{1}H NMR ($CDCl_3$) δ 2.06 (3H, s); 2.08−2.28 (2H, m); 2.36 (2H, d, J = 5.0 Hz); 2.49−2.56 (1H, m); 2.81−3.04 (1H, m); 3.07−3.14 (1H, m); 3.59 and 3.82 (2H, 2 × d, J = 13.8 Hz); 4.50 and 4.57 (2H, 2 × dd, J = 11.9, 6.1, 5.8 Hz); 7.21−7.54 (9H, m). ^{13}C NMR ($CDCl_3$) δ 21.5 (CH_3); 35.0 (CH_2); 37.0 (CH_2); 38.6 (C); 44.6 (CH_2N); 56.0 (CH); 57.7 (CH_2); 62.6 (CH_2); 123.9 (C); 126.2 (CH); 128.6 (CH); 129.2 (CH); 129.8 (CH); 130.0 (CH); 132.8 (C); 137.6 (C); 139.3 (C); 170.8 (C). IR (cm^{-1}): ν_{CO} = 1736 ν_{CN} = 2232. MS (70 eV): m/z (%): 383/5 (M^+ + 1, 100).

Synthesis of *cis*-1-(4-Chlorobenzyl)-2-hydroxymethyl-4-phenylpiperidine-4-carbonitrile, 24. To a solution of *cis*-2-acetoxymethyl-1-(4-chlorobenzyl)-4-phenylpiperidine-4-carbonitrile **22b** and *cis*-6-acetoxy-1-(4-chlorobenzyl)-4-phenylazepane-4-carbonitriles **21b** (0.6 mmol) in methanol (10 mL) was added lithium hydroxide (1.3 mmol, 2 equiv), and the resulting solution was heated under reflux for 2 h. The reaction mixture was poured into water (10 mL) and extracted with Et_2O (3 × 10 mL). Drying ($MgSO_4$), filtration of the drying agent, and evaporation of the solvent in vacuo afforded a mixture of *cis*-1-(4-chlorobenzyl)-6-hydroxy-4-phenylazepane-4-carbonitrile **23** and *cis*-1-(4-chlorobenzyl)-2-hydroxymethyl-4-phenylpiperidin-4-carbonitrile **24** in a ratio of 33−36/64−67 (**23**/**24**). The major isomer *cis*-1-(4-chlorobenzyl)-2-hydroxymethyl-4-phenylpiperidin-4-carbonitrile **24** was isolated and purified by means of column chromatography on silica gel (hexane/EtOAc 1/1).

***cis*-1-(4-Chlorobenzyl)-2-hydroxymethyl-4-phenylpiperidine-4-carbonitrile, 24:** (55%) yellow oil. R_f = 0.34 (hexane/EtOAc 1/1). ^{1}H NMR ($CDCl_3$) δ 2.10 (1H, ddd, J = 13.8, 7.2, 2.8 Hz); 2.29−2.40 (3H, m); 2.50 (1H, ddd, J = 13.4, 7.2, 3.2 Hz); 2.91 (1H, pent., J = 5.6 Hz); 3.03 (1H, ddd, J = 13.4, 8.7, 2.8 Hz); 3.51 and 3.89 (2H, 2 × d, J = 13.5 Hz); 3.88 and 4.00 (2H, 2 × dd, J = 11.6, 6.1, 5.5 Hz); 7.22−7.50 (9H, m). ^{13}C NMR ($CDCl_3$) δ 33.0 (CH_2); 35.1 (CH_2); 38.4 (C); 44.4 (CH_2); 57.4 (CH); 58.1 (CH_2); 60.9 (CH_2); 124.3 (C); 126.4 (CH); 128.4 (CH); 128.8 (CH); 129.3 (CH); 130.0 (CH); 133.2 (C); 137.2 (C); 138.9 (C). IR (cm^{-1}): ν_{OH} = 3435 ν_{CN} = 2232. MS (70 eV): m/z (%): 341/3 (M^+ + 1, 100). Anal. Calcd for $C_{20}H_{21}ClN_2O$: C 70.48; H 6.21; N 8.22. Found: C 70.69; H 6.44; N 8.05.

Synthesis of *trans*-1-(4-Chlorobenzyl)-6-hydroxy-4-phenylazepane-4-carbonitrile, 27. To a solution of *trans*-1-(4-chlorobenzyl)-2-chloromethyl-4-phenylpiperidine-4-carbonitrile **11c** (0.95 mmol) in ethanol (10 mL) was added sodium acetate (1.9 mmol, 2 equiv), and the resulting solution was heated under reflux for 13 h. The reaction mixture was poured into water (10 mL) and extracted with Et_2O (3 × 10 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded *trans*-6-acetoxy-1-(4-chlorobenzyl)-4-phenylazepane-4-carbonitrile **25** and *trans*-2-acetoxymethyl-1-(4-chlorobenzyl)-4-phenylpiperidin-4-carbonitrile **26** in a ratio of 71−79/21−29 (**25**/**26**). Subsequently, acetates **25** and **26** were redissolved in MeOH, after which lithium hydroxide (1.3 mmol, 2 equiv) was added and the resulting solution was heated under reflux for 1 h. Afterward, the reaction mixture was poured into water (10 mL) and extracted with Et_2O (3 × 10 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent in vacuo afforded a mixture of *trans*-1-(4-chlorobenzyl)-6-hydroxy-4-phenylazepane-4-carbonitrile **27** and *trans*-1-(4-chlorobenzyl)-2-hydroxymethyl-4-phenylpiperidin-4-carbonitrile **28** in a 71−79/21−29 (**27**/**28**) ratio. The major constituent, *trans*-1-(4-chlorobenzyl)-6-hydroxy-4-phenylazepane-4-carbonitrile **27**, was isolated in pure form by means of column chromatography on silica gel (hexane/EtOAc 1/1).

Alternative procedure: To a solution of *trans*-1-(4-chlorobenzyl)-2-chloromethyl-4-phenylpiperidine-4-carbonitrile **11c** (0.95 mmol) in ethanol (10 mL), sodium acetate (1.9 mmol, 2 equiv) was added, and the resulting solution was placed in an 80-mL sealed glass vessel, provided with an appropriate stirring bar, and subjected to microwave conditions (110 °C, 20 min). Afterward, the reaction mixture was poured into water (10 mL) and extracted with Et_2O (3 × 10 mL). Drying ($MgSO_4$), filtration of the drying agent, and evaporation of the solvent in vacuo afforded *trans*-6-acetoxy-1-(4-chlorobenzyl)-4-phenylazepane-4-carbonitrile **25** and *trans*-2-acetoxymethyl-1-(4-chlorobenzyl)-4-phenylpiperidin-4-carbonitrile **26** in a ratio of 71−79:21−29 (**25**/**26**). Subsequently, acetates **25** and **26** were redissolved in MeOH, after which lithium hydroxide (1.3 mmol, 2 equiv) was added, and the resulting solution was heated under reflux for 1 h. Afterward, the reaction mixture was poured into water (10 mL) and extracted with Et_2O (3 × 10 mL). Drying ($MgSO_4$), filtration of the drying agent, and evaporation of the solvent in vacuo afforded a mixture of *trans*-1-(4-chlorobenzyl)-6-hydroxy-4-phenylazepane-4-carbonitrile, **27**, and *trans*-1-(4-chlorobenzyl)-2-hydroxymethyl-4-phenylpiperidin-4-carbonitrile, **28**, in a ratio of 71−79:21−29 (**27**/**28**). The major constituent, *trans*-1-(4-chlorobenzyl)-6-hydroxy-4-phenylazepane-4-carbonitrile, **27**, was isolated in pure form by means of column chromatography on silica gel (hexane/EtOAc 1/1).

***trans*-1-(4-Chlorobenzyl)-6-hydroxy-4-phenylazepane-4-carbonitrile, 27:** (55%) yellow oil. R_f = 0.29 (hexane/EtOAc, 3:1). ^{1}H NMR ($CDCl_3$) δ 2.02−2.07 (2H, m); 2.15−2.40 (2H, m); 2.41 (1H, dd, J = 14.3, 5.0, 1.1 Hz); 2.83−2.91 (3H, m); 3.01 (1H, dd, J = 13.2, 3.3 Hz); 3.65 (1H, d, J = 13.5 Hz); 3.71 (1H, d, J = 13.5 Hz); 4.06−4.17 (1H, m); 7.24−7.51 (9H, m). ^{13}C NMR ($CDCl_3$) δ 40.7 (CH_2); 43.6 (C); 47.7 (CH_2); 52.8 (CH_2); 59.8 (CH_2); 62.6 (CH_2); 68.3 (CH); 122.6 (C); 125.2 (CH); 127.9 (CH); 128.7 (CH); 129.2 (CH); 130.4 (CH); 133.1 (C); 137.5 (C); 142.6 (C). IR (cm^{-1}): ν_{OH} = 3422 ν_{CN} = 2236. MS (70 eV): m/z (%): 341/3 (M^+ + 1, 100). Anal. Calcd for $C_{20}H_{21}ClN_2O$: C 70.48; H 6.21; N 8.22. Found: C 70.74; H 6.49; N 8.08.

***trans*-1-(4-Chlorobenzyl)-2-hydroxymethyl-4-phenylpiperidine-4-carbonitrile, 28.** Spectral data were derived from a mixture of nitriles **27** and **28**. Yellow oil. R_f = 0.16 (hexane/EtOAc, 9:1). ^{1}H NMR ($CDCl_3$) δ 1.92−2.10 (2H, m); 2.36 (2H, d, J = 5.0 Hz); 2.55 (1H, dt, J = 11.7, 4.0 Hz); 2.78−3.01 (2H, m); 3.16 (1H, d, J = 13.8 Hz); 3.51 (1H, d (broad), J = 11.0 Hz); 3.98 (1H, dd, J = 11.0, 3.3 Hz); 4.17 (1H, d, J = 13.8 Hz); 7.23−7.49 (9H, m). ^{13}C NMR ($CDCl_3$) δ 35.7 (CH_2); 39.8 (CH_2); 43.0 (C); 49.6 (CH_2); 57.0 (CH_2); 60.0 (CH); 62.9 (CH_2); 122.2 (C); 125.6 (CH); 128.4 (CH); 128.8 (CH); 129.2 (CH); 130.3 (CH); 133.1 (C); 137.0 (C); 139.9 (C). IR (cm^{-1}): ν_{OH} = 3423 ν_{CN} = 2234. MS (70 eV): m/z (%): 341/3 (M^+ + 1, 100).

Synthesis of 2-Arylmethyl-5-phenyl-2,7-diazabicyclo[3.3.1]-nonanes, 29. As a representative example, the synthesis of 2-(4-methylbenzyl)-5-phenyl-2,7-diazabicyclo[3.3.1]nonane **29b** is described here. To a solution of *cis*-1-(4-methylbenzyl)-2-chloromethyl-4-phenylpiperidine-4-carbonitrile **9b** (0.6 mmol) in dry THF (10 mL), $LiAlH_4$ (1.2 mmol, 2 equiv) was added and the resulting solution was heated under reflux for 2 h under nitrogen atmosphere. The reaction mixture was poured into water (10 mL) and extracted with Et_2O (3 × 10 mL). Drying ($MgSO_4$), filtration of the drying agent, and evaporation of the solvent in vacuo afforded 2-(4-methylbenzyl)-5-phenyl-2,7-diazabicyclo-[3.3.1]nonane **29b**, which was purified through crystallization from Et_2O/hexane (1/1).

2-(4-Methylbenzyl)-5-phenyl-2,7-diazabicyclo[3.3.1]nonane, 29b: (75%) white crystals. Mp = 110.3 °C. ^{1}H NMR ($CDCl_3$) δ 1.92−2.03 (2H, m); 2.13−2.27 (2H, m); 2.34 (3H, s); 2.65

(1H, dd, J = 12.9, 1.9 Hz); 2.80−2.90 (3H, m); 3.27 (1H, dd, J = 12.7, 2.8 Hz); 3.39−3.49 (2H, m); 3.73 (1H, d, J = 13.2 Hz); 3.78 (1H, d, J = 13.2 Hz); 7.11−7.36 (9H, m). ^{13}C NMR ($CDCl_3$) δ 21.3 (CH_3); 35.4 (C); 37.1 (CH_2); 37.4 (CH_2); 46.4 (CH_2); 49.7 (CH_2); 52.1 (CH); 58.7 (CH_2); 60.0 (CH_2); 125.1 (CH); 126.1 (CH); 128.4 (CH); 128.9 (CH); 129.1 (CH); 136.5 (C); 136.6 (C); 149.2 (C). IR (cm^{-1}): ν_{NH2} = 3336. MS (70 eV): m/z (%): 307 ($M^+ + 1$, 100). Anal. Calcd for $C_{21}H_{26}N_2$: C 82.31; H 8.55; N 9.14. Found: C 82.39; H 8.63; N 9.02.

Synthesis of *tert*-Butyl 2-(4-methylbenzyl)-5-phenyl-2,7-diazabicyclo[3.3.1]nonane-7-carboxylate, 30. To a solution of 2-(4-methylbenzyl)-5-phenyl-2,7-diazabicyclo[3.3.1]nonane **29b** (0.2 mmol) in dry CH_2Cl_2 (10 mL), Boc_2O (0.22 mmol, 1.1 equiv), pyridine (0.22 mmol, 1.1 equiv) and DMAP (0.022 mmol, 0.1 equiv) were added, and the resulting solution was stirred at room temperature for 3 h. The reaction mixture was poured into brine (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). Drying ($MgSO_4$), filtration of the drying agent,and evaporation of the solvent in vacuo afforded *tert*-butyl 2-(4-methylbenzyl)-5-phenyl-2,7-diazabicyclo[3.3.1]nonane-7-carboxylate,**30**, which was isolated in pure form by means of column chromatography on silica gel (hexane/EtOAc, 3:1).

***tert*-Butyl 2-(4-Methylbenzyl)-5-phenyl-2,7-diazabicyclo[3.3.1]-nonane-7-carboxylate, 30:** (90%) yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.57 (9H, s); 1.82−2.03 (2H, m); 2.11−2.25 (2H, m); 2.33 (3H, s); 2.63−2.81 (3H, m); 2.96−3.07 (2H, m); 3.75 (2H, 2 × d, J = 14.3 Hz); 4.55 (2H, d, J = 13.2 Hz); 7.12−7.38 (9H, m). ^{13}C NMR ($CDCl_3$) δ 21.2 (CH_3); 28.9 (CH_3); 35.5 (C); 37.0 (CH_2); 38.0 (CH_2); 42.8 (CH_2); 48.1 (CH_2); 50.8 (CH); 53.2 (CH_2); 60.0 (CH_2); 79.8 (C); 125.2 (CH); 126.6 (CH); 128.6 (CH); 128.8 (CH); 129.2 (CH); 136.0 (C); 136.7 (C); 147.4 (C); 154.3 (C). IR (cm^{-1}): ν_{CO} = 1687. MS (70 eV): m/z (%): 407 ($M^+ + 1$, 100). Anal. Calcd for $C_{26}H_{34}N_2O_2$: C 76.81; H 8.43; N 6.89. Found: C 77.06; H 8.71; N 6.98.

Synthesis of *trans*-4-Aminomethyl-1-arylmethyl-2-methyl-4-phenylpiperidine, 31. As a representative example, the synthesis of *trans*-4-aminomethyl-2-methyl-1-(4-methylbenzyl)-4-phenylpiperidine **31b** is described here. To a solution of *trans*-2-chloromethyl-1-(4-methylbenzyl)-4-phenylpiperidine-4-carbonitrile **11b** (0.6 mmol) in dry THF (10 mL), $LiAlH_4$ (1.2 mmol, 2 equiv) was added and the resulting solution was heated under reflux for 2 h under nitrogen atmosphere. The reaction mixture was poured into water (10 mL) and extracted with Et_2O (3 × 10 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded *trans*-4-aminomethyl-2-methyl-1-(4-methylbenzyl)-4-phenylpiperidine, **31b**, which was isolated in pure form by means of column chromatography on silica gel (CH_2Cl_2/MeOH 94/6).

***trans*-4-Aminomethyl-2-methyl-1-(4-methylbenzyl)-4-phenylpiperidine, 31b:** (65%) yellow oil. R_f = 0.06 (CH_2Cl_2/MeOH, 94:6). ^{1}H NMR ($CDCl_3$) δ 1.23 (1H, d, J = 6.1 Hz); 1.67 (1H, dd, J = 13.2, 11.6 Hz); 1.81 (1H, dt, J = 13.1, 3.8 Hz); 2.00 (1H, dd, J = 13.2, 2.8 Hz); 2.07 (1H, dt, J = 13.1, 2.5 Hz); 2.24 (1H, dt, J = 12.1, 2.5 Hz); 2.33 (3H, s); 2.54−2.60 (1H, m); 2.75 (1H, dt, J = 12.1, 3.8 Hz); 2.92 and 2.98 (2H, 2 × d, J = 12.9 Hz); 3.17 (2H, d, J = 13.2 Hz); 4.08 (2H, d, J = 13.2 Hz); 7.10−7.34 (9H, m). ^{13}C NMR ($CDCl_3$) δ 21.2 (CH_3); 21.6 (CH_3); 32.3 (CH_2); 41.0 (C); 42.6 (CH_2); 47.5 (CH_2); 48.2 (CH_2); 52.5 (CH); 57.8 (CH_2); 125.9 (CH); 126.1 (CH); 128.4 (CH); 129.0 (CH); 129.2 (CH); 135.9 (C); 136.5 (C); 147.6 (C). IR (cm^{-1}): ν_{NH2} = 3370. MS (70 eV): m/z (%): 309 ($M^+ + 1$, 100). Anal. Calcd for $C_{21}H_{28}N_2$: C 81.77; H 9.15; N 9.08. Found: C 81.95; H 9.32; N 8.98.

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Supporting Information Available: Spectroscopic data of compounds **6b**,**c**, **7b**,**c**, **9b**,**c**, **11b**,**c**, **21a**, **22a**, **29a**,**c**, and **31a**. This material is available free of charge via the Internet at http://pubs.acs.org.