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Stereoselective Synthesis of *cis*-3,4-Disubstituted Piperidines through Ring Transformation of 2-(2-Mesyloxyethyl)azetidines

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Supporting Information

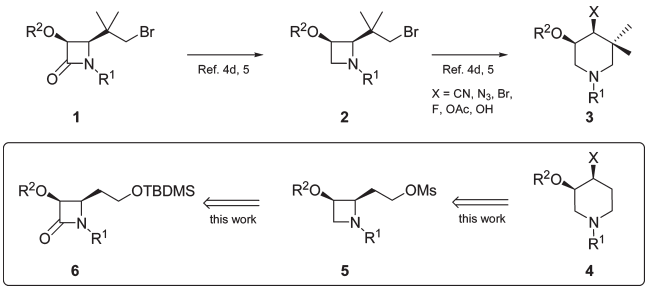
ABSTRACT: The reactivity of 2-(2-mesyloxyethyl)azetidines, obtained through monochloroalane reduction and mesylation of the corresponding β-lactams, with regard to different nucleophiles was evaluated for the first time, resulting in the stereoselective preparation of a variety of new 4-acetoxy-, 4-hydroxy-, 4-bromo-, and 4-formyloxypiperidines. During these reactions, transient 1-azoniabicyclo[2.2.0]hexanes were prone to undergo an S_N2-type ring opening to afford the final azaheterocycles, which was rationalized by means of a detailed computational analysis. This approach constitutes a convenient alternative for the known preparation of 3,4-disubstituted 5,5-dimethylpiperidines, providing an easy access to the 5,5-nor-dimethyl analogues as valuable templates in medicinal chemistry. Furthermore, *cis*-4-bromo-3-(phenoxy or benzyloxy)piperidines were elaborated into the piperidin-3-one framework via dehydrobromination followed by acid hydrolysis.

INTRODUCTION

Substituted six-membered azaheterocycles in general and piperidines in particular are found in a whole variety of natural products and pharmaceutical compounds and continue to attract considerable attention due to their diverse and important biological activities. The pivotal position of piperidines is illustrated by the fact that several thousands of piperidine derivatives have been mentioned in clinical or preclinical studies.[1] The biological importance of this ring system makes short and versatile routes to substituted piperidines of high interest and value. Therefore, a continuous interest exists in the development of new methodologies for the synthesis of biologically active piperidines.[2]

Within azaheterocyclic chemistry, azetidines are an extraordinary class of strained compounds, which makes them excellent candidates for nucleophilic ring-opening or ring-expansion reactions yielding highly substituted acyclic amines or higher ring systems. As a result, substituted azetidines have, for example, been proven to be suitable starting materials for rearrangements toward pyrroles, pyrrolidines, pyrrolidinones, imidazolidinones, isoxazolidines, piperidines, 1,2-oxazines, piperidin-2-ones, 2-iminopiperidines, azepanes, and azepan-2-ones.[3] Moreover, the introduction of a leaving group in one of the substituents of these small-ring heterocycles enables intramolecular transformations toward intermediate bicyclic azetidinium ions, which are subsequently prone to undergo ring opening (mostly implying ring expansion) by the expelled leaving group or by an additional nucleophile.[4,5]

Scheme 1



In previous work, we have demonstrated the applicability of 2-(2-bromo-1,1-dimethylethyl)azetidines **2**, prepared via monochloroalane reduction of the corresponding β-lactams **1**, for the construction of stereodefined 4-cyano-, 4-azido-, 4-bromo-, 4-fluoro-, 4-acetoxy-, and 4-hydroxypiperidines **3** (Scheme 1).[4d,5a] The starting β-lactams **1** were synthesized through Staudinger reaction of *N*-(3-bromo-2,2-dimethylpropylidene)amines and the appropriate ketenes. Nonetheless, the incorporation of a 5,5-*gem*-dimethyl group in piperidines **3** hampered the further elaboration of this synthetic methodology, as the corresponding 5,5-nor-dimethyl variants are usually considered to be more effective in terms of biological activities.

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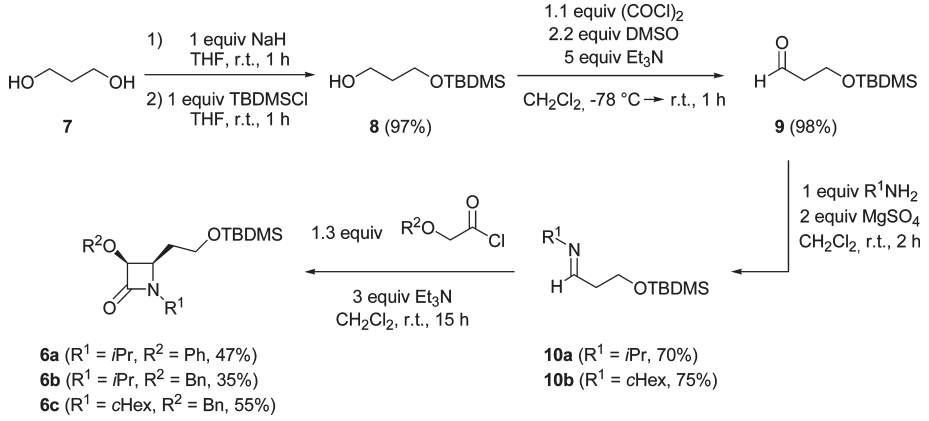
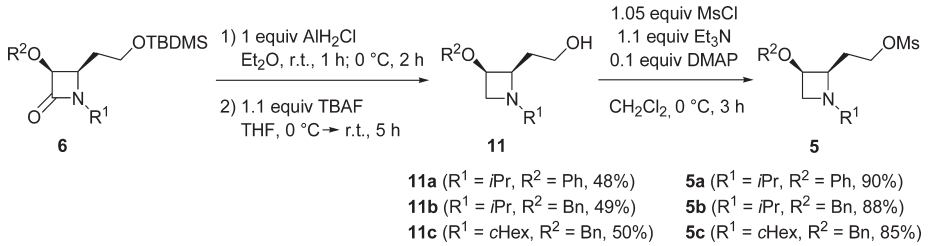
Scheme 2



Scheme 3



In that respect, the synthesis of analogous piperidines **4**, in which no 5,5-*gem*-dimethyl group is present (Scheme 1), might open up interesting possibilities for the development of biologically and pharmaceutically relevant compounds. To achieve this goal, a different synthetic route had to be developed, as the presence of α-protons in the *N*-(3-bromopropylidene)amines leads to dehydrobromination as an undesired side reaction. From a retrosynthetic point of view, the synthesis and ring expansion of 2-(2-mesyloxyethyl)azetidines, prepared via mesylation of the corresponding alcohols, could offer a convenient alternative and an easy access to this new class of 5-unsubstituted piperidines. The present paper will focus on the reactivity of different nucleophiles with regard to 2-(2-mesyloxyethyl)azetidines **5** to develop new pathways toward biologically relevant piperidines. Hereby, it should be noted that the chemistry of 2-(2-hydroxyethyl)azetidines has been explored to a very limited extent up to now, apart from reports of one type in which the (unsubstituted) 2-azetidinylethanol moiety was found to contribute significantly to the functional activity of nonpeptide GnRH (gonadotropin releasing hormone) antagonists, thus imparting to their clinical efficacy for the treatment of several diseases including prostate cancer and breast cancer.[6]

RESULTS AND DISCUSSION

To achieve a selective oxidation and to circumvent difficulties associated with the presence of a free hydroxyl group during β-lactam formation, 1,3-propanediol **7** was first monoprotected as its *tert*-butyldimethylsilyl ether **8** using a literature protocol, involving silylation of the monosodium salt (obtained upon treatment of diol **7** with 1 equiv of NaH in THF) with 1 equiv of *tert*-butyldimethylsilyl chloride (TBDMSCl) in THF,[7] and then oxidized to the corresponding aldehyde **9** by means of a Swern oxidation using oxalyl chloride, DMSO, and Et_3N in CH_2Cl_2 (Scheme 2).[8] Subsequent imination of 3-(*tert*-butyldimethylsilyloxy)propanal **9** with 1 equiv of isopropylamine or cyclohexylamine in dichloromethane in the presence of $MgSO_4$ as a drying agent led to the formation of (*E*)-*N*-[3-(*tert*-butyldimethylsilyloxy)propylidene]alkylamines **10a,b** in high yields. Subsequently, imines **10** were used as substrates for a Staudinger reaction upon treatment with 1.3 equiv of two different acetyl chlorides (i.e., phenoxy- and benzyloxyacetyl chloride) in the presence of 3 equiv of triethylamine in dichloromethane, affording the corresponding novel *cis*-4-[2-(*tert*-butyldimethylsilyloxy)ethyl]azetidin-2-ones **6** (together with small amounts (17−33%) of the corresponding *N*-alkyl-*N*-[3-(*tert*-butyldimethylsilyloxy)prop-1-enyl]acetamides) after 15 h at room temperature (Scheme 2). This reaction involves a [2 + 2] cycloondensation of imines **10** with the ketenes in situ generated from benzyloxy- and phenoxyacetyl chloride. The stereochemical outcome of the Staudinger reaction toward azetidin-2-ones **6** was shown to be *cis* based on the coupling constants between the protons at C3 and C4 in ^{1}H NMR (4.1−4.7 Hz, $CDCl_3$).[9] It should be noted that the reported yields are yields obtained after purification by column chromatography on silica gel.

Although the chemistry of β-lactams has been thoroughly investigated in the past,[10] very little is known about the synthetic applicability of the latter class of 2-azetidinones **6**, pointing at the unexplored nature of this subject. Indeed, β-lactams **6** hold interesting potential for further elaboration due to the presence of a strained four-membered ring and an oxygenated carbon center. Therefore, a thorough investigation was executed to reveal the synthetic applicability of these new β-lactam scaffolds.

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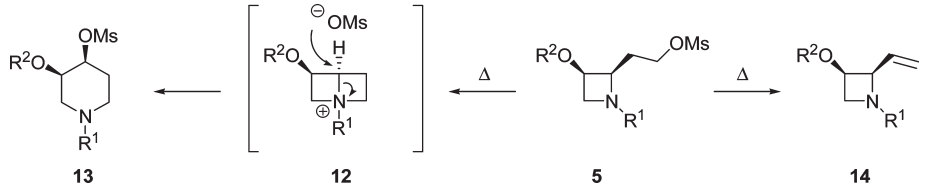
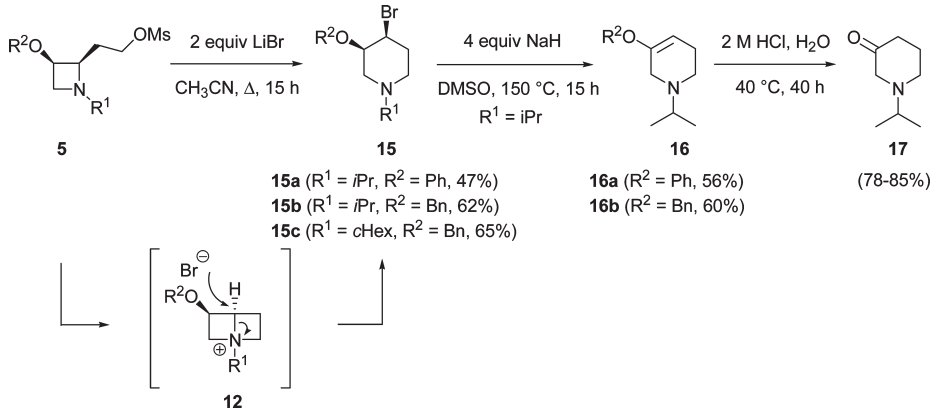
Scheme 4



Scheme 5



To perform a selective reduction of the carbonyl moiety without affecting the four-membered ring system, β-lactams **6** were treated with monochloroalane (AlH_2Cl), as this method had already been proven to be a suitable method for the synthesis of functionalized azetidines.[4,5a,11] Also in the present report, reductions of highly functionalized β-lactams **6** were performed successfully in that respect. Treatment of β-lactams **6** with 1 molar equiv of AlH_2Cl, prepared in situ from 3 molar equiv of $LiAlH_4$ and 1 equiv of $AlCl_3$, in Et_2O at 0 °C for 2 h furnished the corresponding 2-(2-hydroxyethyl)azetidines **11** in good yields after deprotection of the silyl ether using 1.1 equiv of tetra-*n*-butylammonium fluoride (TBAF) in THF (Scheme 3). It has to be noted that in all cases significant amounts of alcohols **11** (40−85%) were present in the crude reaction mixtures after monochloroalane reduction of the corresponding β-lactams **6** without subsequent introduction of TBAF. Furthermore, it was necessary to perform an inverse addition by adding β-lactams **6** to 1 molar equiv of AlH_2Cl in diethyl ether.

The reductive removal of the carbonyl group in β-lactams **6** proceeded with retention of stereochemistry as defined during the Staudinger synthesis of these β-lactams **6**. The *cis* stereochemistry of azetidines **11** was unambiguously proven by the observation that the coupling constants between the protons at C2 and C3 of the azetidine ring (6.6−7.7 Hz, ^{1}H NMR, $CDCl_3$) were similar to coupling constants found in the literature for azetidines with analogous stereochemistry.[4d,5,11c]

Azetidines are generally recognized as valuable four-membered ring systems in organic chemistry, both from a synthetic[3−5,12] and from a medicinal viewpoint.[13] Also, 2-(2-hydroxyethyl)azetidines **11** were expected to furnish a broad range of reactivities, although little has been reported on the synthesis and reactivity of this type of functionalized azetidines.

Consequently, the aptitude of 2-(2-mesyloxyethyl)azetidines **5**, synthesized in high yields by treatment of azetidines **11** with 1.05 equiv of mesyl chloride (MsCl) in the presence of a base and a catalytic amount of 4-(dimethylamino)pyridine (DMAP) in dichloromethane at 0 °C for 3 h (Scheme 3), as substrates for ring expansion toward piperidine derivatives was evaluated with the intention to provide a convenient entry into the biologically relevant class of 3-oxygenated piperidines. Although the ring expansion of functionalized azetidines to produce 2-unsubstituted pyrrolidines is known in the literature,[4a,f] a similar rearrangement of azetidines toward 5,6-unsubstituted piperidines has not been described before.

It should be stressed that during workup of the obtained mesylated azetidines **5**, careful monitoring of the temperature proved to be very important, as evaporation of the solvent *in vacuo* at temperatures higher than 25 °C led to the spontaneous formation of reasonable amounts (4−35%) of ring-expanded 4-mesyloxypiperidines **13**, which can be explained considering the formation and subsequent mesylate-induced ring opening of intermediate 1-azoniabicyclo[2.2.0]hexanes **12**. In addition, small amounts of 2-vinylazetidines **14** (3−12%) were observed as well (Scheme 4).

In the next part, the deployment of azetidines **5** for the synthesis of 4-substituted piperidines was examined. Thus, treatment of 2-(2-mesyloxyethyl)azetidines **5** with 2 equiv of LiBr in acetonitrile for 15 h under reflux resulted in the selective formation of *cis*-4-bromopiperidines **15** in high yields after column chromatography on silica gel or recrystallization from absolute ethanol (Scheme 5). The *cis* stereochemistry of 3-oxygenated 4-bromopiperidines **15** was assessed on the basis of the coupling constants between the protons at position 3 and 4 (3.6−3.9 Hz, ^{1}H NMR, $CDCl_3$), which are in accordance with those reported in the literature for *cis*-vicinal substituted piperidines.[5a,14] Furthermore, the fact that dehydrobromination occurred upon treatment of piperidines **15a,b** with dimsylsodium (four equiv) in DMSO at 150 °C for 15 h was indicative of

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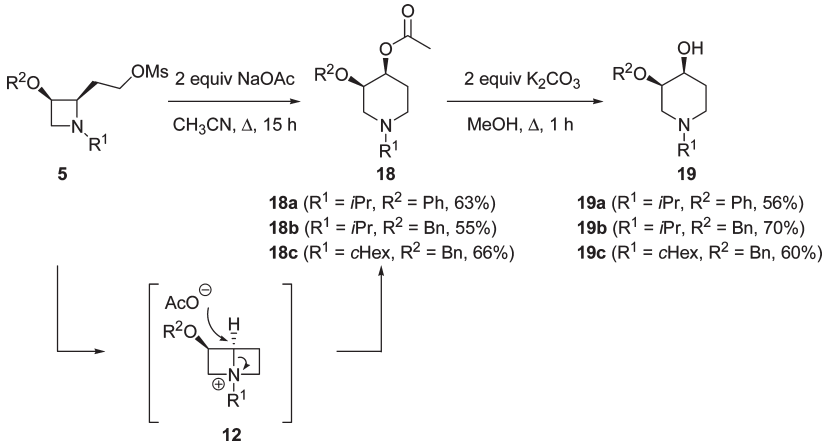
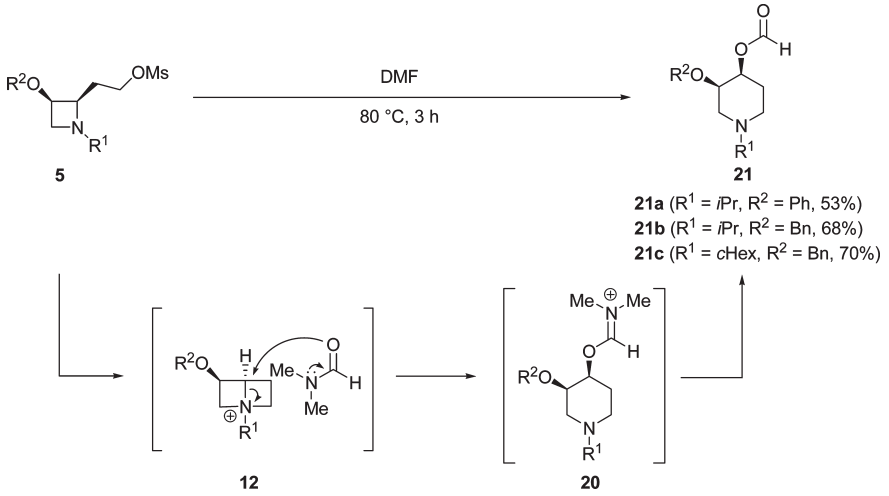
Scheme 6



Scheme 7



a *cis* relationship between the C3 and C4 substituents, which is required to obtain an *anti*-elimination (Scheme 5). The obtained cyclic enol ethers **16** could be easily hydrolyzed to give 1-isopropylpiperidin-3-one **17**[15] by reaction with aq 2 M HCl at 40 °C for 40 h (Scheme 5). Piperidin-3-ones constitute a class of compounds of high biological interest as they are considered as pharmacophores in medicinal sciences and their synthesis is often associated with the preparation of biologically relevant compounds.[16]

From a mechanistic point of view, the observed *cis* stereochemistry of piperidines **15** can be rationalized considering the in situ formation and consecutive ring opening of bicyclic azetidinium intermediates **12** (Scheme 5). This reaction mechanism is based on the intramolecular displacement of the mesyloxy substituent by the nucleophilic nitrogen lone pair of azetidines **5** toward reactive bicyclic intermediates **12**, which are subsequently prone to undergo ring opening by a nucleophile, i.e., bromide, at the bridgehead carbon atom in an S_N2 fashion to furnish the thermodynamically more favored six-membered 4-bromopiperidines **15** (Scheme 5). It should be stressed that the transient generation of 1-azoniabicyclo[2.2.0]hexanes has been described in only a few exceptional cases in the literature so far.[4d,5a] An alternative reaction pathway, involving direct nucleophilic substitution of the mesyloxy group by bromide followed by ring expansion via bicyclic azetidinium ions **12**, should not be excluded. The selective formation of 4-bromopiperidines **15** over 4-mesyloxypiperidines **13** can be attributed to the considerably stronger nucleophilicity of bromide in acetonitrile as compared to the mesyloxy anion.

Upon detailed spectroscopic analysis, small amounts of 2-vinylazetidines **14** (5−9%) were observed as well in the crude reaction mixtures, as characteristic azetidine chemical shifts and typical signals for vinylic protons were detected in the ^{1}H NMR spectra of these mixtures ($CDCl_3$).

Subsequently, attempts were made to broaden the scope of this synthetic methodology toward other 4-substituted piperidine derivatives. The possibility of introducing nucleophiles other than bromine was first tested through the addition of sodium acetate. Thus, treatment of azetidines **5** with 2 equiv of NaOAc in acetonitrile under reflux for 15 h resulted in the selective formation of *cis*-4-acetoxypiperidines **18** in good yields (Scheme 6). The relative *cis* stereochemistry controlled by the Staudinger synthesis of β-lactams **6** was transferred through the reaction sequence, affording *cis*-piperidines **18** in a stereoselective way as demonstrated by the vicinal coupling constants between the protons at C3 and C4 (2.9−4.0 Hz,

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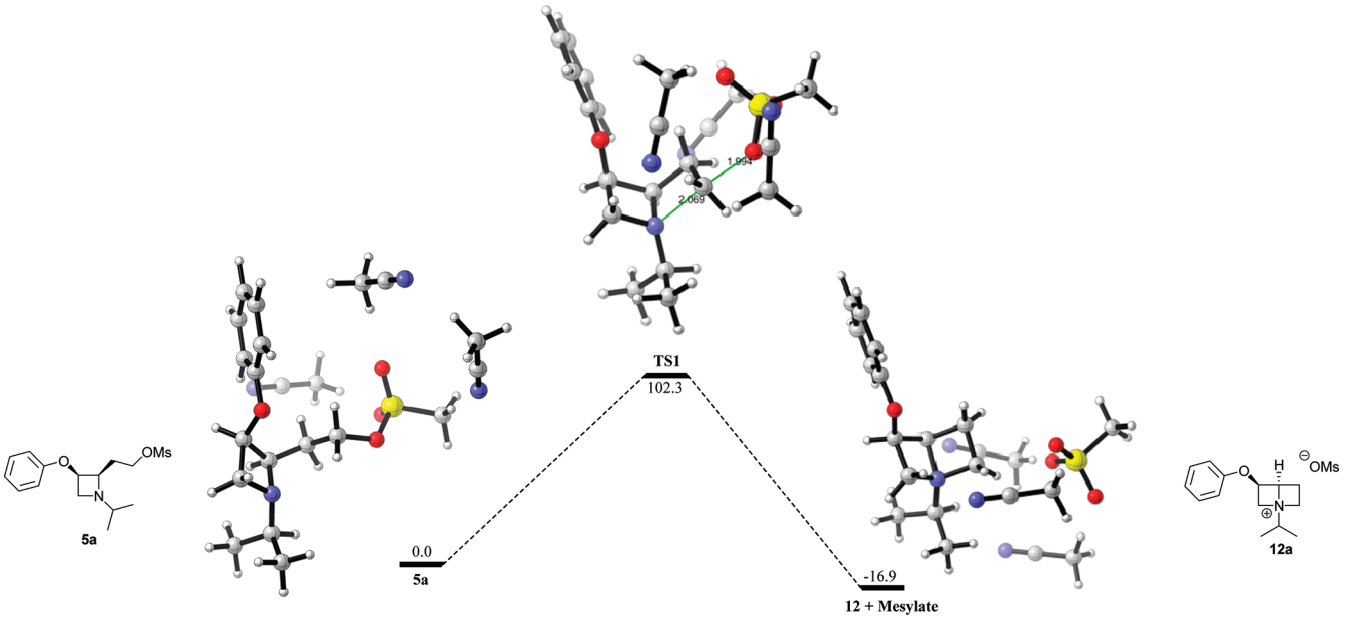

Figure 1. Formation of the bicyclic azetidinium ion **12a**, solvated by explicit acetonitrile molecules. M06-2X/6-311++G(d,p)//B3LYP/6-31+G(d,p). Critical distances in Å.

^{1}H NMR, $CDCl_3$), which are in accordance with literature data concerning *cis*-3,4-dioxygenated piperidines.[5a,14] Again, small amounts of 2-vinylazetidines **14** (2−6%) were present in the crude reaction mixtures.

Next, the reactivity of 4-acetoxypiperidines **18** was evaluated with the intention to provide a convenient entry into the biologically relevant class of 4-hydroxylated piperidines,[17] yielding the corresponding *cis*-4-hydroxy-3-(phenoxy- or benzyloxy) piperidines **19** via methanolysis of the ester moiety upon treatment with 2 equiv of K_2CO_3 in methanol under reflux for 1 h (Scheme 6).

To further assess their intrinsic reactivity, azetidines **5** were heated in DMF at 80 °C for 3 h. Surprisingly, next to small amounts of 2-vinylazetidines **14** (3−7%), azetidines **5** were almost exclusively converted into *cis*-4-formyloxypiperidines **21** (Scheme 7). A plausible explanation for this transformation involves the formation of intermediate azetidinium salts **12**, followed by nucleophilic ring opening by dimethylformamide at the bridgehead carbon atom. Subsequent hydrolysis of intermediates **20** during aqueous workup afforded the corresponding piperidines **21** in high yields after purification by column chromatography on silica gel. Again, the relative *cis* stereochemistry obtained during the Staudinger synthesis of β-lactams **6** was retained, thus affording *cis*-piperidines **21** as can be derived from the coupling constants between the protons at C3 and C4 (3.9−4.1 Hz, ^{1}H NMR, $CDCl_3$).[5a,14]

In addition to the elegant nature of this transformation (no additional reagents required), 4-formyloxypiperidines thus obtained are valuable compounds due to the combination of a piperidine moiety and a formyloxy group, which enables the preparation of a variety of functionalized piperidines through further modification of the ester functionality.

THEORETICAL RATIONALIZATION

The *cis* stereochemistry observed in piperidines formed from the ring enlargement of azetidines **5** can be rationalized by the formation of intermediate bicyclic azetidinium ions **12**. To assess the feasibility of this process and the relative stability of these intermediates, a density functional theory (DFT)-based computational study was performed on both the formation of the highly transient intermediate **12a** as well as its ring opening by nucleophiles, acetate in particular (Scheme 6), leading to the corresponding piperidine **18a**.

Computational Methodology. DFT calculations, utilizing the Gaussian 09[18] program package, were carried out to model both reactions mentioned above. All reactants, transition states, intermediates, and products were optimized using the hybrid functional B3LYP[19] with the 6-31+G(d,p) basis set.[20] Harmonic vibrational frequencies, computed at the same level of theory, were used to provide thermal contributions to Gibbs free energies at 298 K and 1 atm and to confirm the nature of the stationary points. Intrinsic reaction coordinate (IRC)[21] paths were traced to locate the two associated minima, corresponding to reactant and product complexes, directly connected to each transition state on the potential energy surfaces.

In an effort to investigate the influence of the level of theory on barrier heights, energies were refined with contemporary DFT functionals, including newly developed range-separated hybrids. The following functionals were used in conjunction with the 6-311++G(d,p) basis set: Boese and Martin's τ-dependent hybrid functional BMK,[22] which was especially developed for reaction kinetics and known to efficiently reproduce activation barriers;[23] Truhlar and Zhao's meta hybrid functional M06-2X,[24] which has double the amount of nonlocal exchange and has proven to perform well on organic systems with dispersive effects;[25] CAM-B3LYP, Handy's long-range corrected version of B3LYP utilizing the Coulomb-attenuating method;[26] and finally ω-B97X-D, Head-Gordon's latest hybrid functional, which includes long-range corrections as well as damped atom−atom dispersion corrections,[27] found to be one of the most promising methods in a recent benchmark of density functional methods for main group thermochemistry, kinetics, and noncovalent

interactions[28] and for distance dependent hydrogen-bonded interactions.[29]

Ionic species, such as the nucleophile and nucleophuge involved in nucleophilic substitution reactions, are known to be stabilized by the solvent environment.[30] To properly model the effect of the solvent, a mixed explicit/implicit solvation scheme[31] has been employed in the current study. Explicit solvation, also known as "microsolvation", involves placing discrete solvent molecules around the chemically active species to form a so-called "supermolecule" structure. However, this method only takes into account short-range interactions. To account for potential long-range interactions with the solvent environment, the supermolecule was also immersed in a dielectric continuum by means of the self-consistent reaction field (SCRF) theory.[32] Free energies in acetonitrile (MeCN, ε = 36.6) were obtained via C-PCM, the conductor-like polarizable continuum model,[33] and SMD,[34] the newly developed universal solvation model based on full solute electron densities. The molecular cavity was built, including explicit hydrogen spheres, using atomic radii from the UFF force field scaled by 1.1.

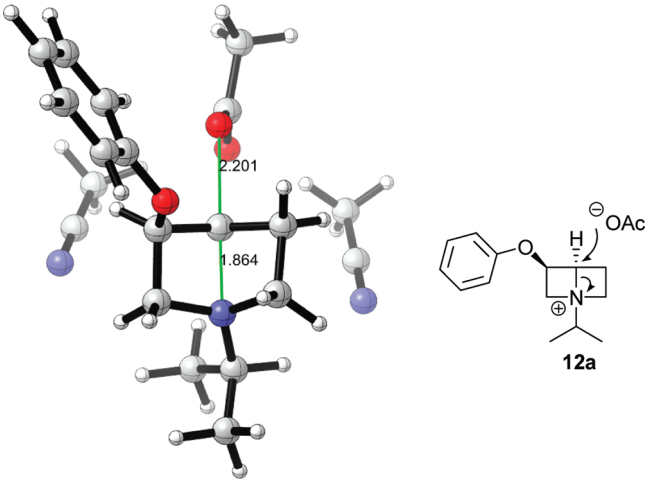

Figure 2. Transition state structure (**TS2**) for the acetate-induced ring opening of bicyclic azetidinium ion **12a**, solvated by explicit acetonitrile molecules. B3LYP/6-31+G(d,p) geometries. Critical distances in Å.

Formation and Ring Opening of Bicyclic Azetidinium Ion 12a. The formation of bicyclic azetidinium ion **12a** (Schemes 4, 5, 6, and 7) occurs via intramolecular nucleophilic attack of the nitrogen atom of the azetidine **5a** (Scheme 3) and simultaneous displacement of the mesylate ion as depicted in **TS1** (Figure 1). Three explicit acetonitrile molecules were used to stabilize the nucleophuge, each interacting with one of the mesylate oxygen atoms through charge−dipole interactions. Typical distances for CH···O type interactions between acetonitrile and the mesylate group are within the range of 2.1−2.3 Å. Ring opening of the bicyclic azetidinium ion **12a** occurs via nucleophilic attack at the bridgehead carbon atom, resulting in the formation of **18a** (Scheme 6), as shown in **TS2** (Figure 2). The incoming acetate ion is stabilized by explicit interactions with two acetonitrile molecules. Interactions between acetonitrile molecules and the acetate ion are similar to those described for the mesylate group. Relative free energies for the formation of bicyclic intermediate **12a** and its ring opening via acetate attack are listed in Table 1.

As mentioned earlier, relative free energies along the reaction path for the formation and ring opening of bicyclic intermediate **12a** were calculated using two different solvation schemes, namely, microsolvation (explicit solvation) and mixed solvation (explicit/implicit solvation). For the latter scheme, two different continuum models (C-PCM and SMD) were employed. For all three solvation models, energies were refined using five different DFT methods, two of which are recently developed range-separated density functionals (CAM-B3LYP and ωB97X-D), that are particularly chosen to account for the long-range dispersive interactions between the substrate and the explicit acetonitrile molecules. Compared to nonsolvated gas-phase results [relative free energy of **TS1** in gas phase =136.6 kJ/mol, BMK/6-311++G(d,p)//B3LYP/6-31+G(d,p)], explicit solvation lowers barriers by an average of 15 kJ/mol by means of stabilizing the forming charge through intermolecular interactions. Results for

Table 1. Relative Gibbs Free Energies (kJ/mol, 298 K and 1 atm) for the Formation and the Nucleophilic Ring Opening of Bicyclic Azetidinium Intermediate 12a[a]

		formation of intermediate **12a**			ring opening of intermediate **12a**		
		5a	**TS1**	**12a** + mesylate	**12a** + acetate	**TS2**	**18a**
explicit solvation	B3LYP	0.0	123.2	26.1	0.0	37.6	−141.1
	BMK	0.0	124.8	1.4	0.0	60.4	−120.3
	M06-2X	0.0	121.1	6.8	0.0	52.8	−142.6
	CAM-B3LYP	0.0	127.2	17.3	0.0	47.6	−141.4
	ωB97X-D	0.0	111.2	−1.8	0.0	57.6	−118.6
explicit/implicit solvation with C-PCM	B3LYP	0.0	104.3	3.4	0.0	43.8	−134.9
	BMK	0.0	105.9	−21.4	0.0	65.4	−114.7
	M06-2X	0.0	102.3	−16.9	0.0	58.5	−135.3
	CAM-B3LYP	0.0	108.1	−5.7	0.0	53.1	−135.3
	ωB97X-D	0.0	92.2	−25.0	0.0	63.3	−111.9
explicit/implicit solvation with SMD	B3LYP	0.0	103.3	−2.7	0.0	45.1	−135.3
	BMK	0.0	105.5	−26.8	0.0	66.2	−116.1
	M06-2X	0.0	102.2	−22.1	0.0	59.2	−136.8
	CAM-B3LYP	0.0	107.3	−11.6	0.0	54.2	−136.2
	ωB97X-D	0.0	91.8	−30.4	0.0	64.2	−113.1

[a] B3LYP/6-31+G(d,p) optimized structures. Single point energy calculations at all levels of theory with 6-311++G(d,p) basis set. Implicit solvation in acetonitrile, ε = 36.6.

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both mixed (explicit/implicit) solvation models, i.e., C-PCM and SMD, indicate that implicit solvation lowers the barriers by an additional 20 kJ/mol, bringing the barrier for the formation of bicyclic intermediate **12a** (see relative energy of **TS1**) down to ~100 kJ/mol. The consistency among C-PCM and SMD results is noteworthy. The ωB97X-D functional, considered to be one of the most promising methods in recent benchmark studies,[28,29] produces on average 10 kJ/mol lower relative free energies compared to other functionals. These results indicate that the formation of intermediate **12a** is a feasible process and, furthermore, its stability is comparable to the starting azetidine **5a**. Nucleophilic ring opening (**TS2**) of the bicyclic azetidinium ion **12a** occurs readily, as illustrated in the small barriers and highly exergonic nature of this reaction step (Table 1).

The nucleophile (acetate) and nucleophuge (mesyloxy) involved in this computational study both bear highly localized negative charges on their oxygen atoms. The solvent, acetonitrile, in return is highly polar (ε = 36.6) yet aprotic and, therefore, is unlikely to form very strong explicit interactions with the substrate. However, the dielectric constant of the solvent body can have a larger stabilizing effect on these charged species, as was observed in this study. Previous computational studies employing the mixed explicit/implicit solvent approach have shown that with protic solvents, such as acetic acid and methanol, microsolvation alone gives sufficient solvent stabilization and the effect of placing the supermolecule in a continuum does not result in any appreciable stabilization.[31d,e] This is in line with the fact that protic solvents give rise to much higher coordination solvation energies per solvent molecule than polar aprotic solvents, due to strong intermolecular hydrogen-bonding interactions.[31f] Nonetheless, the results of this study show that in case of a highly polar aprotic solvent, such as acetonitrile, stabilization caused by the dielectric continuum can be even higher than that caused by explicit charge−dipole interactions between the solvent and the substrate. While microsolvation alone is quite satisfactory for protic solvents, this study has shown that mixed solvation models are necessary to properly mimic the stabilizing effect of highly polar aprotic solvents.

CONCLUSION

In conclusion, the reactivity of 2-(2-mesyloxyethyl)azetidines, prepared via monochloroalane reduction and mesylation of the corresponding β-lactams, toward different nucleophiles has been evaluated for the first time, pointing to a useful transformation of the former into the biologically relevant class of *cis*-3,4-disubstituted piperidines through S_N2 ring opening of intermediate 1-azoniabicyclo[2.2.0]hexanes. The latter bicyclic azetidinium salts, lacking a 5,5-*gem*-dimethyl group, have not yet been described in the literature, and the present results allow the construction of a wide variety of vicinally functionalized six-membered heterocycles. This approach constitutes a convenient alternative for the known preparation of 3,4-disubstituted 5,5-dimethylpiperidines, as the corresponding 5,5-nor-dimethyl variants provide interesting opportunities within the field of drug development. Furthermore, a new entry into the piperidin-3-one scaffold is provided through dehydrobromination of 4-bromo-3-(phenoxy- or benzyloxy)piperidines followed by acid hydrolysis. In addition to the experimental results, the intermediacy of transient 1-azoniabicyclo[2.2.0]hexanes in this transformation was further validated by means of high-level computational analysis. These results show that the bicyclic intermediate could be localized on the potential energy surface as a stable species.

EXPERIMENTAL SECTION

Synthesis of (*E*)-*N*-[3-(*tert*-Butyldimethylsilyloxy)propylidene] alkylamines 10. As a representative example, the synthesis of (*E*)-*N*-[3-(*tert*-butyldimethylsilyloxy)propylidene]isopropylamine **10a** is described here. To a solution of 3-(*tert*-butyldimethylsilyloxy)propanal **9** (10 mmol) in anhydrous CH_2Cl_2 (40 mL) were added $MgSO_4$ (20 mmol, 2 equiv) and isoproylamine (10 mmol, 1 equiv). After 2 h of stirring at room temperature, $MgSO_4$ was removed by filtration. After evaporation of the solvent in vacuo, (*E*)-*N*-[3-(*tert*-butyldimethylsilyloxy)propylidene]isopropylamine **10a** was obtained in 70% yield. Imines **10** were obtained in high purity (>95% based on ^{1}H NMR) and used as such in the next reaction step due to their hydrolytic instability.

(*E*)-*N*-[3-(*tert*-Butyldimethylsilyloxy)propylidene]isopropylamine 10a. (70%) Yellow oil. ^{1}H NMR ($CDCl_3$): δ −0.05 (6H, s); 0.79 (9H, s); 1.05 (6H, d, *J* = 6.3 Hz); 2.34 (2H, q, *J* = 5.8 Hz); 3.19 (1H, septet, *J* = 6.3 Hz); 3.73 (2H, t, *J* = 5.8 Hz); 7.63 (1H, t, *J* = 5.8 Hz). ^{13}C NMR ($CDCl_3$): δ −5.4 (CH_3); 18.2 (C); 24.1 (CH_3); 25.9 (CH_3); 38.9 (CH_2); 60.5 (CH_2); 61.5 (CH); 160.1 (CH). IR (cm^{-1}): $\nu_{C=N}$ = 1666. MS: *m*/*z* (%): 229 (M^+, 1); 214 (10); 172 (100); 142 (14); 130 (35); 100 (32); 73 (18); 59 (9); 43(10).

(*E*)-*N*-[3-(*tert*-Butyldimethylsilyloxy)propylidene]cyclohexylamine 10b. (75%) Yellow oil. ^{1}H NMR ($CDCl_3$): δ 0.05 (6H, s); 0.89 (9H, s); 1.09−1.37, 1.40−1.53, 1.61−1.66 and 1.71−1.82 (10H, 4 × m); 2.44 (2H, q, *J* = 5.7 Hz); 2.88−2.98 (1H, m); 3.83 (2H, t, *J* = 5.7 Hz); 7.74 (1H, t, *J* = 5.7 Hz). ^{13}C NMR ($CDCl_3$): δ −5.3 (CH_3); 18.3 (C); 24.9 (CH_2); 25.2 (CH_2); 25.7 (CH_2); 25.9 (CH_3); 34.4 (CH_2); 36.3 (CH_2); 39.2 (CH_2); 60.7 (CH_2); 69.9 (CH); 160.5 (CH). IR (cm^{-1}): $\nu_{C=N}$ = 1667. MS: *m*/*z* (%): 270 (M^+ + 1, 100).

Synthesis of *cis*-1-Alkyl-4-[2-(*tert*-butyldimethylsilyloxy) ethyl]azetidin-2-ones 6. As a representative example, the synthesis of *cis*-4-[2-(*tert*-butyldimethylsilyloxy)ethyl]-1-isopropyl-3-phenoxyazetidin-2-one **6a** is described here. To an ice-cooled solution of (*E*)-*N*-[3-(*tert*-butyldimethylsilyloxy)propylidene]isopropylamine **10a** (3.6 mmol) and Et_3N (10.8 mmol, 3 equiv) in anhydrous CH_2Cl_2 (25 mL) was added dropwise a solution of phenoxyacetyl chloride (4.7 mmol, 1.3 equiv). The reaction mixture was stirred for 15 h at room temperature and was then washed with water (25 mL). Subsequently, the aqueous phase was extracted with CH_2Cl_2 (3 × 25 mL), after which the combined organic fractions were dried over $MgSO_4$, followed by removal of the drying agent and evaporation of the solvent in vacuo. Purification by means of column chromatography on silica gel (hexane/EtOAc 6/1) afforded pure *cis*-4-[2-(*tert*-butyldimethylsilyloxy)ethyl]-1-isopropyl-3-phenoxyazetidin-2-one **6a**.

***cis*-4-[2-(*tert*-Butyldimethylsilyloxy)ethyl]-1-isopropyl-3-phenoxyazetidin-2-one 6a.** (47%) Yellow crystals. Mp = 57.2 °C. R_f = 0.14 (hexane/EtOAc 6/1). ^{1}H NMR ($CDCl_3$): δ 0.02 and 0.04 (2 × 3H, 2 × s); 0.89 (9H, s); 1.29 and 1.34 (2 × 3H, 2 × d, *J* = 6.8 Hz); 1.95−2.12 (2H, m); 3.60−3.68 and 3.71−3.78 (2 × 1H, 2 × m); 3.85 (1H, septet, *J* = 6.8 Hz); 4.13 (1H, ddd, *J* = 8.8, 4.1, 4.1 Hz); 5.16 (1H, d, *J* = 4.1 Hz); 6.96−7.11 and 7.26−7.32 (5H, 2 × m). ^{13}C NMR ($CDCl_3$): δ −5.42 (CH_3); −5.37 (CH_3); 18.2 (C); 20.1 (CH_3); 21.8 (CH_3); 25.9 (CH_3); 32.7 (CH_2); 44.6 (CH); 54.3 (CH); 59.7 (CH_2); 79.7 (CH); 115.6 (CH); 122.0 (CH); 129.5 (CH); 157.8 (C); 165.5 (C). IR (cm^{-1}): $\nu_{C=O}$ = 1754. MS: *m*/*z* (%): 364 (M^+ + 1, 100). Anal. Calcd for $C_{20}H_{33}NO_3Si$: C 66.07; H 9.15; N 3.85. Found: C 65.87; H 9.37; N 4.18.

***cis*-3-Benzyloxy-4-[2-(*tert*-butyldimethylsilyloxy)ethyl]-1-isopropylazetidin-2-one 6b.** (35%) Yellow oil. R_f = 0.10 (hexane/EtOAc 6/1). ^{1}H NMR ($CDCl_3$): δ −0.07 and −0.06 (2 × 3H, 2 × s); 0.87 (9H, s); 1.20 and 1.24 (2 × 3H, 2 × d, *J* = 6.6 Hz); 1.91−1.97 (2H,

m); 3.58−3.81 (3H, m); 3.88 (1H, ddd, J = 8.8, 4.7, 4.4 Hz); 4.52 (1H, d, J = 4.7 Hz); 4.65 and 4.87 (2 × 1H, 2 × d, J = 11.9 Hz); 7.23−7.35 (5H, m). ^{13}C NMR ($CDCl_3$): δ −5.4 (CH_3); −5.3 (CH_3); 18.3 (C); 20.1 (CH_3); 21.8 (CH_3); 25.9 (CH_3); 32.6 (CH_2); 44.2 (CH); 53.9 (CH); 59.9 (CH_2); 72.6 (CH_2); 80.6 (CH); 127.8 (CH); 128.1 (CH); 128.4 (CH); 137.5 (C); 167.3 (C). IR (cm^{-1}): $\nu_{C=O}$ = 1747. MS: m/z (%): 378 (M^+ + 1, 100). HRMS (ESI) calcd for $C_{21}H_{36}NO_3Si$ 378.2464 $[M + H]^+$, found 378.2463.

***cis*-3-Benzyloxy-4-[2-(*tert*-butyldimethylsilyloxy)ethyl]-1-cyclohexylazetidin-2-one 6c.** (55%) Colorless oil. R_f = 0.11 (hexane/EtOAc 9/1). ^{1}H NMR ($CDCl_3$): δ 0.00 and 0.01 (2 × 3H, 2 × s); 0.86 (9H, s); 1.04−1.30, 1.34−1.47, 1.52−1.60 and 1.69−2.02 (12H, 4 × m); 3.32−3.42 (1H, m); 3.58−3.83 (2H, m); 3.87 (1H, ddd, J = 8.7, 4.5, 4.0 Hz); 4.52 (1H, d, J = 4.5 Hz); 4.65 and 4.87 (2 × 1H, 2 × d, J = 11.9 Hz); 7.26−7.32 (5H, m). ^{13}C NMR ($CDCl_3$): δ −5.4 (CH_3); −5.3 (CH_3); 18.3 (C); 25.2 (CH_2); 25.3 (CH_2); 25.3 (CH_2); 25.9 (CH_3); 30.5 (CH_2); 31.9 (CH_2); 32.6 (CH_2); 52.1 (CH); 54.1 (CH); 59.8 (CH_2); 72.6 (CH_2); 80.6 (CH); 127.8 (CH); 128.4 (CH); 128.4 (CH); 137.5 (C); 167.3 (C). IR (cm^{-1}): $\nu_{C=O}$ = 1746. MS: m/z (%): 418 (M^+ + 1, 100). HRMS (ESI) calcd for $C_{24}H_{40}NO_3Si$ 418.2777 $[M + H]^+$, found 418.2788.

Synthesis of *cis*-1-Alkyl-2-(2-hydroxyethyl)azetidines 11. As a representative example, the synthesis of *cis*-2-(2-hydroxyethyl)-1-isopropyl-3-phenoxyazetidine **11a** is described here. To a solution of aluminum(III) chloride (8 mmol, 1 equiv) in dry Et_2O (30 mL) was added carefully lithium aluminum hydride (24 mmol, 3 equiv) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. Subsequently, a solution of *cis*-4-[2-(*tert*-butyldimethylsilyloxy)ethyl]-1-isopropyl-3-phenoxyazetidin-2-one **6a** (8 mmol) in dry Et_2O (15 mL) was added slowly, and after the addition was complete, the reaction mixture was stirred for 2 h at 0 °C, after which water (10 mL) was added cautiously at 0 °C in order to neutralize the excess of $LiAlH_4$. Afterward, the reaction mixture was filtered and extracted with Et_2O (3 × 25 mL). Drying ($MgSO_4$), filtration of the drying agent, and removal of the solvent afforded a mixture of *cis*-2-[2-(*tert*-butyldimethylsilyloxy)ethyl]-1-isopropyl-3-phenoxyazetidine and *cis*-2-(2-hydroxyethyl)-1-isopropyl-3-phenoxyazetidine **11a**. In the next step, TBAF (8.8 mmol, 1.1 equiv) was added to an ice-cooled solution of the latter reaction mixture in THF (30 mL), and the resulting solution was stirred at room temperature for 5 h. Subsequently, the reaction mixture was poured into brine and extracted with CH_2Cl_2 (3 × 25 mL), after which the organic fraction was dried ($MgSO_4$), followed by removal of the drying agent and evaporation of the solvent in vacuo. Purification by means of column chromatography on silica gel (CH_2Cl_2/MeOH 95/5) afforded pure *cis*-2-(2-hydroxyethyl)-1-isopropyl-3-phenoxyazetidine **11a**.

***cis*-2-(2-Hydroxyethyl)-1-isopropyl-3-phenoxyazetidine 11a.** (48%) White crystals. Mp = 70.2 °C. R_f = 0.10 (CH_2Cl_2/MeOH 95/5). ^{1}H NMR ($CDCl_3$): δ 0.96 and 1.07 (2 × 3H, 2 × d, J = 6.2 Hz); 1.83−1.92 (1H, m); 2.18−2.35 (1H, m); 2.56 (1H, septet, J = 6.2 Hz); 3.28 (1H, dd, J = 9.9, 7.7 Hz); 3.62 (1H, ddd, J = 9.9, 2.9, 1.1 Hz); 3.70−3.79 (2H, m); 4.07 (1H, ddd, J = 11.7, 8.1, 2.9 Hz); 4.91 (1H, ddd, J = 7.7, 7.7, 2.9 Hz); 6.76−6.79, 6.93−6.98 and 7.23−7.29 (5H, 3 × m). ^{13}C NMR ($CDCl_3$): δ 20.1 (CH_3); 21.0 (CH_3); 32.2 (CH_2); 56.7 (CH_2); 57.7 (CH); 60.8 (CH_2); 66.0 (CH); 68.8 (CH); 114.9 (CH); 121.1 (CH); 129.5 (CH); 157.2 (C). IR (cm^{-1}): ν_{OH} = 3360. MS: m/z (%): 236 (M^+ + 1, 100). Anal. Calcd for $C_{14}H_{21}NO_2$: C 71.46; H 8.99; N 5.95. Found: C 71.72; H 9.31; N 5.88.

***cis*-3-Benzyloxy-2-(2-hydroxyethyl)-1-isopropylazetidine 11b.** (49%) White crystals. Mp = 76.3 °C. R_f = 0.10 (CH_2Cl_2/MeOH 95/5). ^{1}H NMR ($CDCl_3$): δ 0.93 and 1.01 (2 × 3H, 2 × d, J = 6.2 Hz); 1.76−1.85 (1H, m); 2.15−2.27 (1H, m); 2.47 (1H, septet, J = 6.2 Hz); 3.04 (1H, dd, J = 9.4, 6.6 Hz); 3.49−3.63 (2H, m); 3.72 (1H, ddd, J = 10.4, 5.1, 4.3 Hz); 3.91 (1H, ddd, J = 10.4, 10.2, 3.0 Hz); 4.25 (1H, ddd, J = 6.6, 6.6, 2.8 Hz); 4.39 and 4.58 (2 × 1H, 2 × d, J = 11.8 Hz); 7.28−7.37 (5H, m). ^{13}C NMR (ref = $CDCl_3$): δ 20.2 (CH_3); 21.1 (CH_3); 32.5 (CH_2); 56.3 (CH_2); 57.6 (CH); 60.8 (CH_2); 67.0 (CH); 70.5 (CH); 70.9 (CH_2); 127.8 (CH); 128.4 (CH); 128.4 (CH); 137.7 (C). IR (cm^{-1}): ν_{OH} = 3380. MS: m/z (%): 250 (M^+ + 1, 100). Anal. Calcd for $C_{15}H_{23}NO_2$: C 72.25; H 9.30; N 5.62. Found: C 72.17; H 9.44; N 5.61.

***cis*-3-Benzyloxy-1-cyclohexyl-2-(2-hydroxyethyl)azetidine 11c.** (50%) White crystals. Mp = 93.3 °C. Recrystallization from hexane/EtOAc (1/25). ^{1}H NMR ($CDCl_3$): δ 0.88−1.28 and 1.61−1.80 (5H and 6H, 2 × m); 2.05−2.15 (1H, m); 2.17−2.26 (1H, m); 3.02 (1H, dd, J = 9.5, 6.5 Hz); 3.55 (1H, dd, J = 9.5, 2.8 Hz); 3.57−3.59 (1H, m); 3.71 (1H, ddd, J = 10.3, 5.1, 5.1 Hz); 3.92 (1H, ddd, J = 10.3, 10.2, 3.1 Hz); 4.26 (1H, ddd, J = 6.6, 6.5, 2.8 Hz); 4.38 and 4.58 (2 × 1H, 2 × d, J = 11.9 Hz); 7.28−7.37 (5H, m). ^{13}C NMR (ref = $CDCl_3$): δ 24.7 (CH_2); 24.8 (CH_2); 25.9 (CH_2); 30.4 (CH_2); 31.5 (CH_2); 32.7 (CH_2); 56.1 (CH_2); 61.0 (CH_2); 66.3 (CH); 66.9 (CH); 71.0 (CH_2); 71.1 (CH); 127.8 (CH); 128.5 (CH); 128.5 (CH); 137.8 (C). IR (cm^{-1}): ν_{OH} = 3147. MS: m/z (%): 290 (M^+ + 1, 100). Anal. Calcd for $C_{18}H_{27}NO_2$: C 74.70; H 9.40; N 4.84. Found: C 74.52; H 9.54; N 4.84.

Synthesis of *cis*-1-Alkyl-2-(2-mesyloxyethyl)azetidines 5. As a representative example, the synthesis of *cis*-1-isopropyl-2-(2-mesyloxyethyl)-3-phenoxyazetidine **5a** is described here. To an ice-cooled solution of *cis*-2-(2-hydroxyethyl)-1-isopropyl-3-phenoxyazetidine **11a** (1 mmol) in CH_2Cl_2 (15 mL) were added 4-(dimethylamino)pyridine (0.1 mmol, 0.1 equiv), Et_3N (1.1 mmol, 1.1 equiv), and mesyl chloride (1.05 mmol, 1.05 equiv), after which the mixture was stirred for 3 h at 0 °C. Afterward, the reaction mixture was washed with brine (2 × 15 mL) and a saturated $NaHCO_3$ solution (2 × 15 mL). The aqueous phase was washed with CH_2Cl_2 (2 × 20 mL). Drying ($MgSO_4$), filtration of the drying agent, and removal of the solvent in vacuo afforded *cis*-1-isopropyl-2-(2-mesyloxyethyl)-3-phenoxyazetidine **5a**. Due to the high intrinsic reactivity of azetidines **5**, no accurate HRMS data could be obtained.

***cis*-1-Isopropyl-2-(2-mesyloxyethyl)-3-phenoxyazetidine 5a.** (90%) Colorless oil. ^{1}H NMR ($CDCl_3$): δ 0.93 and 1.03 (2 × 3H, 2 × d, J = 6.1 Hz); 2.01−2.12 (1H, m); 2.44−2.65 (2H, m); 2.96 (3H, s); 3.19 (1H, dd, J = 9.4, 6.1 Hz); 3.50 (1H, ddd, J = 9.4, 1.9, 1.1 Hz); 3.63 (1H, ddd, J = 10.1, 6.3, 3.4 Hz); 4.25−4.40 (2H, m); 4.83 (1H, ddd, J = 6.3, 6.1, 1.9 Hz); 6.76−6.79, 6.88−7.03 and 7.23−7.34 (5H, 3 × m). ^{13}C NMR (ref = $CDCl_3$): δ 20.0 (CH_3); 21.1 (CH_3); 30.2 (CH_2); 37.3 (CH_3); 56.8 (CH_2); 57.9 (CH); 64.0 (CH); 67.8 (CH_2); 68.0 (CH); 115.1 (CH); 121.3 (CH); 129.7 (CH); 157.1 (C). IR (cm^{-1}): ν_{max} = 2966, 2939, 2872, 1492, 1352, 1234, 1171, 967, 930, 754, 692. MS: m/z (%) 314 (M^+ + 1, 100).

***cis*-3-Benzyloxy-1-isopropyl-2-(2-mesyloxyethyl)azetidine 5b.** (88%) Colorless oil. ^{1}H NMR ($CDCl_3$): δ 0.93 and 0.98 (2 × 3H, 2 × d, J = 6.3 Hz); 1.90−2.01 (1H, m); 2.38−2.53 (2H, m); 2.91 (3H, s); 2.93−3.01 (1H, m); 3.35−3.55 (2H, m); 4.15 (1H, ddd, J = 6.0, 6.0, 1.7 Hz); 4.21−4.35 (2H, m); 4.36 and 4.61 (2 × 1H, 2 × d, J = 12.1 Hz); 7.28−7.37 (5H, m). ^{13}C NMR (ref = $CDCl_3$): δ 20.1 (CH_3); 21.2 (CH_3); 30.1 (CH_2); 37.1 (CH_3); 56.5 (CH_2); 57.9 (CH); 64.4 (CH); 68.3 (CH_2); 69.6 (CH); 70.8 (CH_2); 127.8 (CH); 127.8 (CH); 128.4 (CH); 138.0 (C). IR (cm^{-1}): ν_{max} = 2964, 2931, 2855, 1352, 1172, 960, 925, 813, 735, 698. MS: m/z (%) 328 (M^+ + 1, 100).

***cis*-3-Benzyloxy-1-cyclohexyl-2-(2-mesyloxyethyl)azetidine 5c.** (85%) Yellow oil. ^{1}H NMR ($CDCl_3$): δ 0.99−1.25 and 1.59−1.74 (6H and 4H, 2 × m); 1.90−2.01 and 2.03−2.13 (2 × 1H, 2 × m); 2.41−2.53 (1H, m); 2.90 (3H, s); 2.94−2.98 (1H, m); 3.44−3.51 (2H, m); 4.16 (1H, ddd, J = 6.1, 6.1, 1.1 Hz); 4.21−4.35 (2H, m); 4.36 and 4.61 (2 × 1H, 2 × d, J = 11.9 Hz); 7.28−7.39 (5H, m). ^{13}C NMR (ref = $CDCl_3$): δ 24.6 (CH_2); 24.7 (CH_2); 25.8 (CH_2); 30.1 (CH_2); 30.2 (CH_2); 31.4 (CH_2); 37.1 (CH_3); 56.2 (CH_2); 64.3 (CH_2); 66.4 (CH); 68.4, 70.0, 70.9 (CH, CH, CH_2); 127.8 (CH); 127.9 (CH); 128.4 (CH);

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138.0 (C). IR (cm^{-1}): ν_{max} = 3029, 2927, 2853, 1350, 1172, 969, 921, 812, 734, 699. MS: *m/z* (%) 368 (M^+ + 1, 100).

Synthesis of *cis*-1-Alkyl-4-bromopiperidines 15. As a representative example, the synthesis of *cis*-4-bromo-1-isopropyl-3-phenoxypiperidine **15a** is described here. To a solution of *cis*-1-isopropyl-2-(2-mesyloxyethyl)-3-phenoxyazetidine **5a** (5.5 mmol) in acetonitrile (30 mL) was added LiBr (11 mmol, 2 equiv) at room temperature. After a period of 15 h, the solvent was removed in vacuo, and the residue was extracted with CH_2Cl_2 (1 × 30 mL) and water (2 × 30 mL). The aqueous phase was washed with CH_2Cl_2 (2 × 25 mL). Drying ($MgSO_4$), filtration of the drying agent, and removal of the solvent in vacuo afforded *cis*-4-bromo-1-isopropyl-3-phenoxypiperidine **15a**, which was further purified by column chromatography on silica gel (hexane/EtOAc 9/1).

***cis*-4-Bromo-1-isopropyl-3-phenoxypiperidine 15a.** (47%) Light-yellow oil. R_f = 0.10 (hexane/EtOAc 9/1). ^{1}H NMR ($CDCl_3$): δ 1.06 (6H, d, *J* = 6.6 Hz); 2.17−2.23 (2H, m); 2.60 (1H, d × t, *J* = 11.4, 4.0 Hz); 2.70−2.89 (4H, m); 4.31 (1H, ddd, *J* = 8.5, 4.0, 3.7 Hz); 4.64 (1H, d(broad), *J* = 3.7 Hz); 6.96−7.01 and 7.28−7.33 (5H, 2 × m). ^{13}C NMR ($CDCl_3$): δ 18.1 (CH_3); 18.3 (CH_3); 32.8 (CH_2); 43.9 (CH_2); 48.1 (CH_2); 53.5 (CH); 54.5 (CH); 74.8 (CH); 117.0 (CH); 121.9 (CH); 129.6 (CH); 156.9 (C). IR (cm^{-1}): ν_{max} = 2964, 2828, 2360, 1587, 1492, 1237, 1168, 1059, 752, 690. MS: *m/z* (%): 298/300 (M^+ + 1, 100). HRMS (ESI) calcd for $C_{14}H_{21}BrNO$ 298.0807 $[M + H]^+$, found 298.0797.

***cis*-3-Benzyloxy-4-bromo-1-isopropylpiperidine 15b.** (62%) White crystals. Mp = 79.9 °C. Recrystallization from absolute EtOH. ^{1}H NMR ($CDCl_3$): δ 1.03 and 1.04 (2 × 3H, 2 × d, *J* = 6.6 Hz); 2.02−2.21 (2H, m); 2.52−2.69 (4H, m); 2.76 (1H, septet, *J* = 6.6 Hz); 3.47 (1H, ddd, *J* = 8.3, 3.9, 3.9 Hz); 4.52 (1H, d, *J* = 11.9 Hz); 4.62 (1H, s(broad)); 4.69 (1H, d, *J* = 11.9 Hz); 7.28−7.40 (5H, m). ^{13}C NMR (ref = $CDCl_3$): δ 18.2 (CH_3); 18.4 (CH_3); 32.7 (CH_2); 44.0 (CH_2); 48.6 (CH_2); 54.5 (CH); 54.7 (CH); 70.4 (CH_2); 75.2 (CH); 127.9 (CH); 128.0 (CH); 128.5 (CH); 138.0 (C). IR (cm^{-1}): ν_{max} = 3400, 3028, 2962, 2824, 1165, 1134, 1116, 1094, 1023, 1004, 750, 697. MS: *m/z* (%): 312/314 (M^+ + 1, 100). Anal. Calcd for $C_{15}H_{22}BrNO$: C 57.70; H 7.10; N 4.49. Found: C 58.10; H 7.34; N 4.48.

***cis*-3-Benzyloxy-4-bromo-1-cyclohexylpiperidine 15c.** (65%) White crystals. Mp = 76.6 °C. R_f = 0.06 (hexane/EtOAc 4/1). ^{1}H NMR ($CDCl_3$): δ 1.05−1.25, 1.60−1.65 and 1.78−1.80 (10H, 3 × m); 2.01−2.20 (2H, m); 2.27−2.37 (1H, m); 2.54−2.62 (1H, m); 2.66−2.78 (3H, m); 3.46 (1H, ddd, *J* = 8.3, 3.9, 3.6 Hz); 4.53 (1H, d, *J* = 12.1 Hz); 4.62 (1H, d(broad), *J* = 3.6 Hz); 4.68 (1H, d, *J* = 12.1 Hz); 7.28−7.39 (5H, m). ^{13}C NMR (ref = $CDCl_3$): δ 26.1 (CH_2); 26.4 (CH_2); 28.7 (CH_2); 29.0 (CH_2); 32.9 (CH_2); 44.4 (CH_2); 49.1 (CH_2); 54.8 (CH); 63.8 (CH); 70.3 (CH_2); 75.3 (CH); 127.8 (CH); 128.0 (CH); 128.5 (CH); 138.1 (C). IR (cm^{-1}): ν_{max} = 3062, 3030, 2926, 2852, 1451, 1202, 1116, 1099, 1026, 948, 734, 696. MS: *m/z* (%): 352/354 (M^+ + 1, 100). Anal. Calcd for $C_{18}H_{26}BrNO$: C 61.36; H 7.44; N 3.98. Found: C 61.57; H 7.77; N 4.10.

Synthesis of 1-Alkyl-1,2,5,6-tetrahydropyridines 16. As a representative example, the synthesis of 1-isopropyl-3-phenoxy-1,2,5,6-tetrahydropyridine **16a** is described here. To a solution of *cis*-4-bromo-1-isopropyl-3-phenoxypiperidine **15a** (4.2 mmol) in DMSO (40 mL) was added NaH (16.8 mmol, 4 equiv, 60% dispersion in mineral oil), after which the resulting suspension was stirred for 15 h at 150 °C. Subsequently, the reaction mixture was poured into water (40 mL) and extracted with Et_2O (3 × 25 mL). Afterward, the organic phase was washed intensively with brine (4 × 30 mL). Drying ($MgSO_4$), filtration of the drying agent, and removal of the solvent in vacuo afforded 1-isopropyl-3-phenoxy-1,2,5,6-tetrahydropyridine **16a**, which was further purified by column chromatography on silica gel (hexane/EtOAc 2/1).

1-Isopropyl-3-phenoxy-1,2,5,6-tetrahydropyridine 16a. (56%) Yellow oil. R_f = 0.08 (hexane/EtOAc 2/1). ^{1}H NMR ($CDCl_3$): δ 1.11 (6H, d, *J* = 6.4 Hz); 2.16−2.21 (2H, m); 2.60 (2H, ~t, *J* = 5.8 Hz); 2.82 (1H, septet, *J* = 6.4 Hz); 3.17 (2H, s(broad)); 4.91−4.94 (1H, m); 7.03−7.10 and 7.29−7.34 (5H, 2 × m). ^{13}C NMR (ref = $CDCl_3$): δ 18.6 (CH_3); 24.4 (CH_2); 45.9 (CH_2); 48.9 (CH_2); 54.0 (CH); 102.7 (CH); 119.5 (CH); 123.3 (CH); 129.6 (CH); 152.1 (C); 155.9 (C). IR (cm^{-1}): $\nu_{C=C}$ = 1685. MS: *m/z* (%): 218 (M^+ + 1, 100). HRMS (ESI) calcd for $C_{14}H_{20}NO$ 218.1545 $[M + H]^+$, found 218.1548.

3-Benzyloxy-1-isopropyl-1,2,5,6-tetrahydropyridine 16b. (60%) Light-brown oil. R_f = 0.04 (hexane/EtOAc 2/1). ^{1}H NMR ($CDCl_3$): δ 1.08 and 1.09 (2 × 3H, 2 × d, *J* = 6.5 Hz); 2.16−2.23 (2H, m); 2.56 (2H, ~t, *J* = 5.5 Hz); 2.77 (1H, septet, *J* = 6.5 Hz); 3.08 (2H, s(broad)); 4.74 (2H, s); 4.77 (1H, t, *J* = 3.3 Hz); 7.27−7.39 (5H, m, C_6H_5). ^{13}C NMR (ref = $CDCl_3$): δ 18.7 (CH_3); 24.5 (CH_2); 46.4 (CH_2); 49.9 (CH_2); 54.0 (CH); 69.0 (CH_2); 92.6 (CH); 127.7 (CH); 127.9 (CH); 128.5 (CH); 137.4 (C); 153.2 (C). IR (cm^{-1}): $\nu_{C=C}$ = 1677. MS: *m/z* (%): 232 (M^+ + 1, 100). HRMS (ESI) calcd for $C_{15}H_{22}NO$ 232.1701 $[M + H]^+$, found 232.1700.

Synthesis of *cis*-4-Acetoxy-1-alkylpiperidines 18. As a representative example, the synthesis of *cis*-4-acetoxy-1-isopropyl-3-phenoxypiperidine **18a** is described here. To a solution of *cis*-1-isopropyl-2-(2-mesyloxyethyl)-3-phenoxyazetidine **5a** (10 mmol) in acetonitrile (50 mL) was added NaOAc (20 mmol, 2 equiv) at room temperature. After a reflux period of 15 h, the solvent was removed in vacuo and the residue was extracted with CH_2Cl_2 (1 × 30 mL) and water (2 × 30 mL). The aqueous phase was washed with CH_2Cl_2 (2 × 25 mL). Drying ($MgSO_4$), filtration of the drying agent, and removal of the solvent in vacuo afforded *cis*-4-acetoxy-1-isopropyl-3-phenoxypiperidine **18a**, which was further purified by column chromatography on silica gel (hexane/EtOAc 2/1).

***cis*-4-Acetoxy-1-isopropyl-3-phenoxypiperidine 18a.** (63%) Colorless oil. R_f = 0.09 (hexane/EtOAc 2/1). ^{1}H NMR ($CDCl_3$): δ 1.04 (6H, d, *J* = 6.1 Hz); 1.76−1.86 (1H, m); 2.06 (3H, s); 1.98−2.14 (1H, m); 2.51−2.64 (2H, m); 2.77−2.89 (3H, m); 4.49 (1H, ddd, *J* = 5.9, 5.9, 2.9 Hz); 5.18−5.20 (1H, m); 6.91−6.98 and 7.23−7.29 (5H, 2 × m). ^{13}C NMR ($CDCl_3$): δ 17.8 (CH_3); 18.6 (CH_3); 21.2 (CH_3); 28.4 (CH_2); 44.5 (CH_2); 48.1 (CH_2); 54.3 (CH); 69.5 (CH); 74.2 (CH); 116.6 (CH); 121.4 (CH); 129.5 (CH); 157.8 (C); 170.5 (C). IR (cm^{-1}): $\nu_{C=O}$ = 1736. MS: *m/z* (%): 278 (M^+ + 1, 100). HRMS (ESI) calcd for $C_{16}H_{24}NO_3$ 278.1756 $[M + H]^+$, found 278.1755.

***cis*-4-Acetoxy-3-benzyloxy-1-isopropylpiperidine 18b.** (55%) Light-yellow oil. R_f = 0.05 (hexane/EtOAc 2/1). ^{1}H NMR ($CDCl_3$): δ 1.03 and 1.04 (2 × 3H, 2 × d, *J* = 6.3 Hz); 1.66−1.77 and 1.91−2.00 (2 × 1H, 2 × m); 2.10 (3H, s); 2.44−2.53 (2H, m); 2.57−2.66 (2H, m); 2.77 (1H, septet, *J* = 6.3 Hz); 3.61 (1H, ddd, *J* = 8.1, 3.9, 3.9 Hz); 4.52 and 4.65 (2 × 1H, 2 × d, *J* = 12.1 Hz); 5.26 (1H, s(broad)); 7.28−7.39 (5H, m). ^{13}C NMR (ref = $CDCl_3$): δ 18.0 (CH_3); 18.6 (CH_3); 21.4 (CH_3); 28.6 (CH_2); 44.1 (CH_2); 48.7 (CH_2); 54.5 (CH); 68.5 (CH); 71.0 (CH_2); 74.9 (CH); 127.7 (CH); 127.9 (CH); 128.5 (CH); 138.4 (C); 170.7 (C). IR (cm^{-1}): $\nu_{C=O}$ = 1735. MS: *m/z* (%): 292 (M^+ + 1, 100). HRMS (ESI) calcd for $C_{17}H_{26}NO_3$ 292.1913 $[M + H]^+$, found 292.1916.

***cis*-4-Acetoxy-3-benzyloxy-1-cyclohexylpiperidine 18c.** Attempts to purify this compound failed. Spectral data are based on ^{1}H NMR and ^{13}C NMR of the crude reaction mixture (purity of **18c**: ~85%), and no HRMS analysis was performed. (66%) Colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.05−1.33, 1.57−1.65 and 1.70−1.84 (4H, 1H and 6H, 3 × m); 1.88−1.99 (1H, m); 2.10 (3H, s); 2.29−2.38 (1H, m); 2.53−2.57 (2H, m); 2.64−2.73 (2H, m); 3.60 (1H, ddd, *J* = 8.4, 4.0, 4.0 Hz); 4.52 and 4.64 (2 × 1H, 2 × d, *J* = 12.1 Hz); 5.25 (1H, s(broad)); 7.23−7.36 (5H, m). ^{13}C NMR (ref = $CDCl_3$): δ 21.4 (CH_3); 22.7 (CH_2); 26.1 (CH_2); 26.4 (CH_2); 28.6 (CH_2); 29.0 (CH_2); 31.7 (CH_2); 44.4 (CH_2); 49.1 (CH_2); 63.7 (CH); 68.5 (CH); 70.9 (CH_2); 74.9 (CH); 127.7 (CH); 127.9 (CH); 128.4 (CH); 138.4 (C); 170.7 (C). IR (cm^{-1}): $\nu_{C=O}$ = 1737. MS: *m/z* (%): 332 (M^+ + 1, 100).

Synthesis of *cis*-1-Alkyl-4-hydroxypiperidines 19. As a representative example, the synthesis of *cis*-4-hydroxy-1-isopropyl-3-phenoxypiperidine **19a** is described here. To a solution of *cis*-4-acetoxy-1-isopropyl-3-phenoxypiperidine **18a** (6 mmol) in methanol (40 mL) was added K_2CO_3 (12 mmol, 2 equiv). After a reflux period of 1 h, the solvent was removed in vacuo, and the residue was extracted with Et_2O (1 × 30 mL) and water (2 × 30 mL). The aqueous phase was washed with Et_2O (2 × 25 mL). Drying ($MgSO_4$), filtration of the drying agent, and removal of the solvent in vacuo afforded *cis*-4-hydroxy-1-isopropyl-3-phenoxypiperidine **19a**, which was further purified by column chromatography on silica gel (hexane/EtOAc 1/2).

***cis*-4-Hydroxy-1-isopropyl-3-phenoxypiperidine 19a.** (56%) Colorless oil. R_f = 0.05 (hexane/EtOAc 1/2). ^{1}H NMR ($CDCl_3$): δ 1.04 (6H, d, J = 6.6 Hz); 1.77−1.88 and 1.94−2.03 (2 × 1H, 2 × m); 2.48−2.70 (4H, m); 2.75−2.85 (2H, m); 4.11−4.15 (1H, m); 4.43 (1H, ddd, J = 9.0, 4.4, 3.1 Hz); 6.95−7.00 and 7.26−7.33 (5H, 2 × m). ^{13}C NMR (ref = $CDCl_3$): δ 18.0 (CH_3); 18.5 (CH_3); 30.6 (CH_2); 43.2 (CH_2); 46.6 (CH_2); 54.5 (CH); 66.4 (CH); 76.1 (CH); 116.3 (CH); 121.6 (CH); 129.7 (CH); 157.2 (C). IR (cm^{-1}): ν_{OH} = 3406. MS: m/z (%): 236 (M^+ + 1, 100). HRMS (ESI) calcd for $C_{14}H_{22}NO_2$ 236.1651 $[M + H]^+$, found 236.1653.

***cis*-3-Benzyloxy-4-hydroxy-1-isopropylpiperidine 19b.** (70%) Colorless oil. R_f = 0.03 (hexane/EtOAc 1/3). ^{1}H NMR ($CDCl_3$): δ 1.02 and 1.04 (2 × 3H, 2 × d, J = 6.7 Hz); 1.63−1.74 and 1.86−1.95 (2 × 1H, 2 × m); 2.34 (1H, s(broad)); 2.39−2.45 (1H, m); 2.49−2.64 (3H, m); 2.76 (1H, septet, J = 6.7 Hz); 3.58 (1H, ddd, J = 8.5, 4.1, 4.1 Hz); 3.98 (1H, s(broad)); 4.58 and 4.63 (2 × 1H, 2 × d, J = 12.1 Hz); 7.28−7.38 (5H, m). ^{13}C NMR (ref = $CDCl_3$): δ 18.0 (CH_3); 18.6 (CH_3); 30.5 (CH_2); 43.3 (CH_2); 47.4 (CH_2); 54.5 (CH); 66.1 (CH); 70.8 (CH_2); 76.9 (CH); 127.9 (CH); 127.9 (CH); 128.6 (CH); 138.3 (C). IR (cm^{-1}): ν_{OH} = 3445. MS: m/z (%): 250 (M^+ + 1, 100). HRMS (ESI) calcd for $C_{15}H_{24}NO_2$ 250.1807 $[M + H]^+$, found 250.1812.

***cis*-3-Benzyloxy-1-cyclohexyl-4-hydroxypiperidine 19c.** Attempts to purify this compound failed. Spectral data are based on ^{1}H NMR and ^{13}C NMR of the crude reaction mixture (purity of **19c**: ∼80%), and no HRMS analysis was performed. (60%) Colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.05−1.29, 1.53−1.73 and 1.74−1.92 (5H, 1H and 6H, 3 × m); 2.28−2.38 (1H, m); 2.44−2.51 (1H, m); 2.56−2.71 (3H, m); 3.58 (1H, ddd, J = 8.5, 4.1, 4.1 Hz); 3.97 (1H, s(broad)); 4.57 and 4.62 (2 × 1H, 2 × d, J = 11.8 Hz); 7.25−7.35 (5H, m). ^{13}C NMR (ref = $CDCl_3$): δ 26.1 (CH_2); 26.2 (CH_2); 26.4 (CH_2); 28.5 (CH_2); 29.1 (CH_2); 30.6 (CH_2); 43.7 (CH_2); 47.7 (CH_2); 63.9 (CH); 66.1 (CH); 70.8 (CH_2); 76.8 (CH); 127.8 (CH); 127.9 (CH); 128.6 (CH); 138.3 (C). IR (cm^{-1}): ν_{OH} = 3428. MS: m/z (%): 290 (M^+ + 1, 100).

Synthesis of *cis*-1-Alkyl-4-formyloxypiperidines 21. As a representative example, the synthesis of *cis*-4-formyloxy-1-isopropyl-3-phenoxypiperidine **21a** is described here. A solution of *cis*-1-isopropyl-2-(2-mesyloxyethyl)-3-phenoxyazetidine **5a** (1 mmol) in DMF (15 mL) was heated at 80 °C for 3 h. Subsequently, the reaction mixture was poured into water (15 mL) and extracted with Et_2O (3 × 15 mL). Afterward, the organic phase was washed intensively with brine (4 × 20 mL). Drying ($MgSO_4$), filtration of the drying agent, and removal of the solvent in vacuo afforded *cis*-4-formyloxy-1-isopropyl-3-phenoxypiperidine **21a**, which was further purified by column chromatography on silica gel (hexane/EtOAc 2/1).

***cis*-4-Formyloxy-1-isopropyl-3-phenoxypiperidine 21a.** (53%) Colorless oil. R_f = 0.07 (hexane/EtOAc 2/1). ^{1}H NMR ($CDCl_3$): δ 1.04 (6H, d, J = 6.1 Hz); 1.82−1.93 and 2.04−2.13 (2 × 1H, 2 × m); 2.57−2.60 (2H, m); 2.70−2.87 (3H, m); 4.49 (1H, ddd, J = 8.4, 4.0, 4.0 Hz); 5.34−5.36 (1H, m); 6.90−6.99 and 7.24−7.31 (5H, 2 × m); 8.14 (1H, s). ^{13}C NMR ($CDCl_3$): δ 17.9 (CH_3); 18.4 (CH_3); 28.7 (CH_2); 43.8 (CH_2); 47.7 (CH_2); 54.4 (CH); 69.2 (CH); 74.0 (CH); 116.3 (CH); 121.6 (CH); 129.6 (CH); 157.3 (C); 160.5 (CH). IR (cm^{-1}): $\nu_{C=O}$ = 1721. MS: m/z (%): 264 (M^+ + 1, 100). HRMS (ESI) calcd for $C_{15}H_{22}NO_3$ 264.1600 $[M + H]^+$, found 264.1602.

***cis*-3-Benzyloxy-4-formyloxy-1-isopropylpiperidine 21b.** (68%) Colorless oil. R_f = 0.06 (hexane/EtOAc 1/2). ^{1}H NMR ($CDCl_3$): δ 1.03 and 1.04 (2 × 3H, 2 × d, J = 6.3 Hz); 1.71−1.82 (1H, m); 1.94−2.02 (1H, m); 2.45−2.63 (3H, m); 2.68−2.72 (1H, m); 2.79 (1H, septet, J = 6.3 Hz); 3.64 (1H, ddd, J = 9.1, 4.1, 4.1 Hz); 4.54 and 4.66 (2 × 1H, 2 × d, J = 11.9 Hz); 5.38 (1H, s(broad)); 7.24−7.39 (5H, m); 8.15 (1H, s). ^{13}C NMR (ref = $CDCl_3$): δ 18.0 (CH_3); 18.5 (CH_3); 28.8 (CH_2); 43.6 (CH_2); 48.4 (CH_2); 54.5 (CH); 68.4 (CH); 71.1 (CH_2); 74.8 (CH); 127.9 (CH); 128.0 (CH); 128.5 (CH); 138.1 (C); 160.7 (CH). IR (cm^{-1}): $\nu_{C=O}$ = 1720. MS: m/z (%): 278 (M^+ + 1, 100). HRMS (ESI) calcd for $C_{16}H_{24}NO_3$ 278.1756 $[M + H]^+$, found 278.1770.

***cis*-3-Benzyloxy-1-cyclohexyl-4-formyloxypiperidine 21c.** (70%) Colorless oil. R_f = 0.06 (hexane/EtOAc 4/1). ^{1}H NMR ($CDCl_3$): δ 1.05−1.28, 1.59−1.66 and 1.73−1.83 (6H, 1H and 4H, 3 × m); 1.92−2.01 (1H, m); 2.29−2.38 (1H, m); 2.54−2.60 (2H, m); 2.63−2.78 (2H, m); 3.62 (1H, ddd, J = 9.0, 3.9, 3.9 Hz); 4.54 and 4.64 (2 × 1H, 2 × d, J = 11.6 Hz); 5.36 (1H, s(broad)); 7.28−7.36 (5H, m); 8.14 (1H, s). ^{13}C NMR (ref = $CDCl_3$): δ 26.1 (CH_2); 26.1 (CH_2); 26.4 (CH_2); 28.6 (CH_2); 28.9 (CH_2); 29.1 (CH_2); 44.0 (CH_2); 48.9 (CH_2); 63.8 (CH); 68.6 (CH); 71.0 (CH_2); 74.9 (CH); 127.8 (CH); 127.9 (CH); 128.5 (CH); 138.2 (C); 160.8 (CH). IR (cm^{-1}): $\nu_{C=O}$ = 1724. MS: m/z (%): 318 (M^+ + 1, 100). HRMS (ESI) calcd for $C_{19}H_{28}NO_3$ 318.2069 $[M + H]^+$, found 318.2077.

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H NMR and ^{13}C NMR spectra of compounds **10a,b**, **6a−c**, **11a−c**, **5a−c**, **15a−c**, **16a,b**, **18a−c**, **19a−c**, and **21a−c**. Cartesian coordinates and energies of the optimized geometries (B3LYP/6-31++G(d,p)) of ground states; Cartesian coordinates, energies, imaginary and low frequencies of the optimized geometries (B3LYP/6-31++G**) of transition states. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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