**Synthesis of piperidin-4-ones starting from 2-(2-bromo-1,1-dimethylethyl)azetidines and 2-(2-mesyloxyethyl)azetidines through a ring expansion-oxidation protocol**

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**Graphical abstract**



**Abstract**

*cis*-2-(2-Bromo-1,1-dimethylethyl)azetidines were transformed into novel 5,5-dimethylpiperidin-4-ones through a ring expansion-oxidation protocol upon heating in DMSO in the presence of Ag2CO3 or AgBF4. In addition, several 5,5-nor-dimethyl analogues of the latter piperidin-4-ones were synthesized in a selective way through a similar ring expansion-oxidation approach involving treatment of *cis*-2-(2-mesyloxyethyl)azetidines with K2CO3 in DMSO. Furthermore, both a diastereoselective and an enantioselective reduction of the carbonyl function in piperidin-4-ones was performed through a chemical and an enzymatic approach, respectively. Whereas the NaBH4-induced reduction proceeded with *cis*-diastereoselectivity, alcohol dehydrogenase-mediated reductions resulted in either an *S*- or *R*-enantioselectivity.

*Keywords*: -lactams, DMSO, ring expansion-oxidation, piperidinones

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1. **Introduction**

The piperidine ring is a ubiquitous structural feature in many alkaloid natural products and drug candidates.[[1]](#endnote-1) Watson et al. have asserted that during a recent 10-year period thousands of piperidine compounds have been mentioned in clinical and preclinical studies.[[2]](#endnote-2) Among them, piperidin-4-ones represent an important class of bioactive heterocycles attracting a progressive interest due to their observed biological and pharmaceutical properties, such as antiviral, antitumor,[[3]](#endnote-3) analgesic,[[4]](#endnote-4) local anaesthetic,[[5]](#endnote-5) antimicrobial, bactericidal, fungicidal, herbicidal, insecticidal, antihistaminic, anti-inflammatory, anticancer, CNS stimulant and depressant activities.[[6]](#endnote-6) Furthermore, piperidin-4-ones have been used as eligible intermediates in the synthesis of a variety of biologically active compounds, including functionalized piperidines, through further modification of the carbonyl moiety.[[7]](#endnote-7)

In the present paper, a new and efficient synthetic methodology toward functionalized piperidin-4-one scaffolds is developed, i.e., a one-step ring enlargement of *cis*-2-(2-bromo-1,1-dimethylethyl)azetidines and *cis*-2-(2-mesyloxyethyl)azetidines to the corresponding piperidin-4-ones through a ring expansion-oxidation protocol upon heating in DMSO in the presence of silver or potassium carbonate or silver tetrafluoroborate. An analogous transformation of 2-(bromomethyl)pyrrolidines into piperidin-3-ones *via* bicyclic aziridinium salts has previously been reported by us,[[8]](#endnote-8) although it should be mentioned that 2-(halomethyl)pyrrolidines are known to undergo rearrangements readily.[[9]](#endnote-9) Nonetheless, this type of transformations is peculiar, as DMSO is known to directly oxidize organic halides to the corresponding carbonyl compounds, as demonstrated amply by the Kornblum reaction and its variants.[[10]](#endnote-10)

In light of the utility of piperidin-4-ones as synthetic intermediates, the stereoselective reduction of the carbonyl functionality in these structures toward the corresponding 4-hydroxypiperidines is investigated by means of both a chemical and a biocatalytic approach. Biologically spoken, the 4-hydroxypiperidine motif is of particular interest due to its presence in a large number of natural products with a range of bioactivities including antiarrhythmic, antituberculosis, antidiarrheal and antischizophrenic activity.[[11]](#endnote-11)

1. **Results and discussion**

Azetidines comprise a valuable class of small-ring azaheterocyclic compounds with often pronounced biological activities.[[12]](#endnote-12) In addition, azetidines have proven to be excellent building blocks for the synthesis of a large variety of ring-opened and ring-expanded systems due to the inherent reactivity of the constrained four-membered ring.[[13]](#endnote-13) In previous work, we have demonstrated the applicability of 2-(2-bromo-1,1-dimethylethyl)azetidines as useful intermediates toward the diastereoselective preparation of 4-cyano-, 4-azido-, 4-bromo-, 4-fluoro-, 4-acetoxy- and 4-hydroxypiperidines[[14]](#endnote-14),[[15]](#endnote-15) and, more recently, we have studied the reactivity of 2-(2-mesyloxyethyl)azetidines for the stereoselective synthesis of 4-acetoxy-, 4-hydroxy-, 4-bromo-, and 4-formyloxypiperidines, thus providing an easy access to the 5,5-nor-dimethyl analogues of the former piperidines.[[16]](#endnote-16)

With the intention to further evaluate the intrinsic reactivity of these classes of azetidines, *cis*-2-(2-bromo-1,1-dimethylethyl)azetidines **1a-d** were treated with five equiv of AgBF4 in DMSO at 100 °C for 18 h,[[17]](#endnote-17) unexpectedly affording piperidin-4-ones **4a-d** in a selective way in good yields and high purity (Scheme 1, Table 1). In order to assess the importance of AgBF4 in this rearrangement, the use of other inorganic salts was then evaluated. Surprisingly, treatment of azetidines **1a-d** with five equiv of K2CO3 in DMSO did not result in the formation of 5,5-dimethylpiperidin-4-ones **4a-d**,8 but instead complex reaction mixtures were obtained. On the other hand, treatment of 1-allyl-3-benzyloxy-2-(2-bromo-1,1-dimethylethyl)azetidine **1a** with five equiv of Ag2CO3 in DMSO at 100 °C for 18 h again afforded the corresponding 1-allyl-3-benzyloxy-5,5-dimethylpiperidin-4-on **4a** in 87% yield. Apparently, the presence of a silver ion is crucial for the selective formation of 5,5-dimethylpiperidin-4-ones **4a-d**. This work comprises the first report of an azetidine to piperidinone ring expansion-oxidation protocol mediated by a silver salt in DMSO.

From a mechanistic point of view, the following rationale can be suggested. Azetidines **1a-d** are first transformed into highly reactive bicyclic azetidinium salts **2a-d** through intramolecular displacement of the bromide by the nitrogen lone pair. The intermediacy of 1-azoniabicylo[2.2.0]hexanes such as **2a-d** in azetidine-to-piperidine rearrangements has previously been established by us, supported by computational analyses.14,15,16 The expelled bromide is unable to induce ring enlargement toward 4-bromopiperidines due to complexation with the silver ion. The necessity of the silver counterion is thus based on trapping of the bromide so that ring transformation toward brominated piperidines is prevented.14,15 The intermediate bicyclic azetidinium salts **2a-d** are subsequently converted into piperidines **3a-d** upon ring enlargement with dimethylsulfoxide, which acts as a nucleophile. Abstraction of the acidic proton at the oxygenated carbon atom results in the liberation of dimethylsulfide and the formation of piperidin-4-ones **4a-d** (Scheme 1). Although no irrefutable proof for this mechanistic approach is provided here, the previously described selective transformation of *cis*-azetidines **1** into different *cis*-piperidines via nucleophile-induced ring opening of strained intermediates **2** supports the proposed mechanistic rationale.14,15,16 An alternative reaction pathway involving initial formation of monocyclic carbenium ion intermediates has been excluded in these previous azetidine-to-piperidine rearrangements, as nucleophilic addition across these cyclic carbenium ions cannot account for the observed *cis*-stereospecificity. However, in this case, an alternative reaction pathway involving monocyclic carbenium ion intermediates cannot be completely excluded. In addition, formation of the corresponding bicyclic oxiranium ion intermediates has been excluded as well in these previous studies, as subsequent nucleophilic ring opening would lead to mixtures of regioisomers.[[18]](#endnote-18)



**Scheme 1**

# Table 1 Synthesis of piperidin-4-ones 4

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Compound | R1 | R2 | R3 | X | Reagent | Yield |
| **4a** | allyl | Bn | Me | Br | AgBF4 | 65% |
| **4a** | allyl | Bn | Me | Br | Ag2CO3 | 87% |
| **4b** | *t*Bu | Bn | Me | Br | AgBF4 | 71% |
| **4c** | *i*Pr | Ph | Me | Br | AgBF4 | 66% |
| **4d** | *c*Hex | Ph | Me | Br | AgBF4 | 63% |
| **4e** | *i*Pr | Ph | H | OMs | K2CO3 | 43% |
| **4f** | *i*Pr | Bn | H | OMs | K2CO3 | 45% |
| **4g** | *c*Hex | Bn | H | OMs | K2CO3 | 48% |

In order to broaden the scope of this synthetic transformation, our interest was directed toward the ring enlargement of *cis*-2-(2-mesyloxyethyl)azetidines **1e-g** *via* a similar ring expansion-oxidation mechanism. In that respect, azetidines **1e-g** were stirred in DMSO at 100 °C for 18 h in the presence of five equiv of K2CO3, resulting in full conversion of the starting material toward the desired piperidin-4-ones **4e-g** in good yields (Scheme 1, Table 1), together with minor amounts of unidentified side products (8-27%). However, when wet DMSO was used, in some cases a substantial amount (up to 70%) of 4-hydroxypiperidines was obtained along with piperidin-4-ones **4e-g** after heating of azetidines **1e-g** in DMSO, which might be the result of an incomplete oxidation reaction or direct hydrolysis of the strained intermediates **2e-g**, probably due to the presence of water in DMSO. Moreover, the addition of K2CO3 appeared to be essential, as piperidin-4-ones **4e-g** were formed in very low yields (5-8%) if the reaction was performed in the absence of K2CO3. In analogy with the above-described reaction mechanism, the initially formed bicyclic azetidinium ions **2e-g** are ring opened by DMSO at the bridgehead carbon atom in an SN2-type fashion to yield piperidines **3e-g**, which are subsequently transformed into the corresponding piperidin-4-ones **4e-g** upon proton abstraction. The preferential formation of piperidin-4-ones **4e-g** over 4-mesyloxypiperidines can be attributed to the relative higher nucleophilicity of DMSO as compared to the mesylate anion, making inactivation of the latter by complexation unnecessary. This stands in contrast with the necessity of a silver salt for the selective ring expansion-oxidation of 2-(2-bromoethyl)azetidines **1a-d** toward piperidin-4-ones **4a-d**.

As mentioned before, the 4-hydroxypiperidine moiety comprises a privileged scaffold that is encountered in many bioactive compounds exhibiting antiarrhythmic,11b,c antidepressant, hypotensive11c and anti-inflammatory activity.11d Furthermore, 4-hydroxypiperidine-containing compounds are used in the treatment of multiple sclerosis,11e rheumatoid arthritis,11e,f Crohn’s disease,11f tuberculosis,11g diarrhea11h and [schizophrenia](http://en.wikipedia.org/wiki/Schizophrenia).11i In that respect, the reduction of piperidin-4-ones **4a-g** was contemplated in the next phase. At first, treatment of piperidin-4-ones **4a-g** with two molar equiv of NaBH4 in MeOH was performed, affording the corresponding *cis*-4-hydroxypiperidines **5a-g**14,16 in 73-90% yield after reflux for two hours (Scheme 2). It should be noted that this NaBH4-mediated reduction of racemic piperidin-4-ones **4a-g** toward 4-hydroxypiperidines **5a-g** proceeded with complete *cis*-diastereoselectivity. The relative *cis*-stereochemistry at positions 3 and 4 is a direct result of the addition of hydride at the carbonyl moiety, governed by steric hindrance exerted by the benzyloxy substituent.



**Scheme 2**

In a second approach, an enzyme-mediated enantioselective reduction of piperidin-4-ones was investigated using alcohol dehydrogenases. The reduction of carbonyl compounds by alcohol dehydrogenases and their cofactors has numerous advantages compared to classical chemical reactions, such as the high level of enantioselectivity and the environmentally-benign reaction conditions, and this field of research has gained an increased relevance over the past few years, especially concerning the synthesis of important intermediates for pharmaceuticals and bioactive compounds.[[19]](#endnote-19) Therefore, a biocatalytic approach was explored in this study as an alternative to the well-established metal-catalyzed asymmetric reductions known in the literature. As a selected example, racemic 3-benzyloxy-1-isopropylpiperidin-4-one **4f** was treated with a commercially available *S*-specific[[20]](#endnote-20) or *R*-specific[[21]](#endnote-21) alcohol dehydrogenase in aqueous MES-buffer [2-(*N*-morpholino)ethanesulfonic acid] at 30 °C in the presence of NADH. In contrast to the chemical reduction process, the merit of this enzymatic approach comprises the *S*- and *R*-enantioselective reduction of the carbonyl functionality, in each case resulting in the formation of two diastereoisomers (ratio 1/1, based on 1H NMR, Scheme 3). The four enantiomers **6**, **7**, **8** and **9** were obtained in analytically pure form in 43-49% yield by separation of the latter diastereoisomeric mixtures through column chromatography on silica gel. In order to establish their enantiomeric ratio, esterification of hydroxypiperidines **6**, **7**, **8** and **9** was performed utilizing one equivalent of (1*S*)-(-)-camphanic chloride in CH2Cl2 at room temperature for 15 hours in the presence of 0.1 equivalents of DMAP [4-(dimethylamino)pyridine] and two equivalents of Et3N, pointing to a diastereoisomeric ratio of 99.4/0.6, 99.4/0.6, 98.1/1.9 and 97.9/2.1 for piperidines **6**, **7**, **8** and **9**, respectively (based on GC/MS-analysis). Consequently, an enantiomeric ratio of 99.4/0.6, 99.4/0.6, 98.1/1.9 and 97.9/2.1 could be assigned to 4-hydroxypiperidines **6**, **7**, **8** and **9** (Scheme 3). The absolute configurations were assigned by comparison of the observed rotation of piperidines **6** (αD = +27.7°, CH2Cl2), **7** (αD = +7.6°, CHCl3), **8** (αD = -7.6°, CHCl3) and **9** (αD = -27.7°, CH2Cl2) with optical rotations described in the literature for similar 3,4-dioxygenated piperidines.[[22]](#endnote-22) Based on these findings, both chemical and enzymatic reductions can be used in a complementary way to affect a diastereoselective or enantioselective synthesis of 4-hydroxypiperidines from piperidin-4-ones, respectively.



**Scheme 3**

1. **Conclusion**

In conclusion, functionalized 5,5-dimethylpiperidin-4-ones were prepared in high yields and purity through a silver-mediated ring expansion-oxidation of the corresponding 2-(2-bromo-1,1-dimethylethyl)azetidines upon treatment with Ag2CO3 or AgBF4 in DMSO at 100 °C. Furthermore, the synthesis of the 5,5-nor-dimethyl variants of the latter piperidin-4-ones was accomplished *via* a similar ring expansion-oxidation of 2-(2-mesyloxyethyl)azetidines upon treatment with K2CO3 in DMSO. This is the first report on the full conversion of functionalized azetidines into piperidin-4-ones. In addition, the synthetic applicability of these novel piperidin-4-ones was demonstrated by means of a chemical and enzymatic reduction, thus affording a straightforward entry into the biologically relevant class of 4-hydroxypiperidines. Whereas the NaBH4-induced reduction is characterized by a *cis*-diastereoselectivity, the alcohol dehydrogenase-mediated reductions proceeded with *S*- or *R*-enantioselectivity at the carbonyl functionality.

1. **Experimental part**
	1. **General**

1H NMR spectra were recorded at 300 MHz (JEOL ECLIPSE+) with CDCl3 as solvent and tetramethylsilane as internal standard. 13C NMR spectra were recorded at 75 MHz (JEOL ECLIPSE+) with CDCl3 as solvent and tetramethylsilane as internal standard. Mass spectra were obtained with a mass spectrometer Agilent 1100, 70 eV. IR spectra were measured with a Spectrum One FT-IR spectrophotometer. Elemental analyses were performed with a Perkin Elmer series II CHNS/O analyzer 2400. High resolution electron spray (ES) mass spectra were obtained with an Agilent Technologies 6210 Series Time-of-Flight. Dichloromethane was distilled over calcium hydride, while diethyl ether was dried over sodium benzophenone ketyl. Other solvents were used as received from the supplier. Melting points of crystalline compounds were measured with a Büchi 540 apparatus.

* 1. **Synthetic procedures**
		1. **Synthesis of piperidin-4-ones 4**

General procedure: To a solution of azetidine **1**14 (10 mmol) in DMSO (40 mL) was added AgBF4, Ag2CO3 or K2CO3 (50 mmol, 5 equiv). After stirring at 100 °C for 18 h, the reaction mixture was poured into water (40 mL) and extracted with diethyl ether (3 × 50 mL). Afterward, the organic phase was washed intensively with brine (4 × 40 mL). Drying (MgSO4), filtration of the drying agent, and removal of the solvent afforded piperidin-4-ones **4**, which were further purified by column chromatography on silica gel.

* + - 1. **1-Allyl-3-benzyloxy-5,5-dimethylpiperidin-4-one 4a**

1H NMR (CDCl3, 300 MHz): *δ* = 1.05 and 1.27 (2 × s, 2 × 3H), 2.11 (d, 1H, *J* = 11.6 Hz), 2.29 (d × d, 1H, *J* = 10.9, 10.5 Hz), 2.70 (d × d, 1H, *J* = 11.6, 2.9 Hz), 2.97-3.14 (m, 2H), 3.28 (d × d × d, 1H, *J* = 10.5, 6.7, 2.9 Hz), 4.31 (d × d, 1H, *J* = 10.9, 6.7 Hz), 4.50 and 4.85 (2 × d, 2 × 1H, *J* = 11.8 Hz), 5.15-5.23 (m, 2H), 5.84 (d × d × t, 1H, *J* = 16.9, 10.3, 6.5 Hz), 7.24-7.41 (m, 5H); 13C NMR (CDCl3, 75 MHz): *δ* = 21.8, 25.1, 45.7, 59.5, 60.4, 65.5, 72.5, 76.9, 118.0, 127.8, 127.9, 128.4, 134.9, 137.8, 211.7; IR (ATR): *ν* = 1723 (C=O); MS (ES+): *m/z* = 274 (MH+). Column chromatography (SiO2), petroleum ether - ethyl acetate 17:1, Rf = 0.14. Yield 65%, colourless oil. HRMS (ESI) calcd for C17H24NO2 274.1807 [M + H]+, found 274.1811.

* + - 1. **3-Benzyloxy-1-*tert*-butyl-5,5-dimethylpiperidin-4-one 4b**

1H NMR (CDCl3, 300 MHz): *δ* = 1.04 and 1.24 (2 × s, 2 × 3H), 1.08 (s, 9H), 2.20 (d, 1H, *J* = 11.6 Hz), 2.31 (d × d, 1H, *J* = 10.5, 10.5 Hz), 2.79 (d × d, 1H, *J* = 11.6, 3.4 Hz), 3.46 (d × d × d, 1H, *J* = 10.5, 6.7, 3.4 Hz), 4.23 (d × d, 1H, *J* = 10.5, 6.7 Hz), 4.48 and 4.86 (2 × d, 2 × 1H, *J* = 11.6 Hz), 7.27-7.42 (m, 5H); 13C NMR (CDCl3, 75 MHz): *δ* = 21.8, 24.9, 26.6, 45.9, 53.2, 53.5, 59.2, 72.6, 78.3, 127.8, 128.0, 128.4, 138.1, 212.6; IR (ATR): *ν* = 1723 (C=O); MS (ES+): *m/z* = 290 (MH+). M.p. = 37.3 °C (column chromatography (SiO2), petroleum ether - ethyl acetate 19:1, Rf = 0.15). Yield 71%, yellow crystals. Anal. Calcd for C18H27NO2: C 74.70, H 9.40, N 4.84. Found: C 74.74, H 9.51, N 4.79.

* + - 1. **1-Isopropyl-5,5-dimethyl-3-phenoxypiperidin-4-one 4c**

1H NMR (CDCl3, 300 MHz): *δ* = 1.05 and 1.06 (2 × d, 2 × 3H, *J* = 6.6 Hz), 1.07 and 1.38 (2 × s, 2 × 3H), 2.37 (d, 1H, *J* = 11.4 Hz), 2.61 (d × d, 1H, *J* = 10.6, 10.5 Hz), 2.67 (d × d, 1H, *J* = 11.4, 3.3 Hz), 2.96 (septet, 1H, *J* = 6.6 Hz), 3.41 (d × d × d, 1H, *J* = 10.5, 6.7, 3.3 Hz), 5.06 (d × d, 1H, *J* = 10.6, 6.7 Hz), 6.76-6.89, 6.92-6.98 and 7.22-7.33 (3 × m, 5H); 13C NMR (CDCl3, 75 MHz): *δ* = 18.0, 18.7, 21.8, 25.0, 46.3, 54.1, 55.2, 61.0, 76.9, 115.4, 121.5, 129.5, 158.0, 209.8; IR (ATR): *ν* = 1728 (C=O); MS (ES+): *m/z* = 262 (MH+). Column chromatography (SiO2), petroleum ether - ethyl acetate 24:1, Rf = 0.15. Yield 66%, colourless oil. HRMS (ESI) calcd for C16H24NO2 262.1807 [M + H]+, found 262.1811.

* + - 1. **1-Cyclohexyl-5,5-dimethyl-3-phenoxypiperidin-4-one 4d**

1H NMR (CDCl3, 300 MHz): *δ* = 1.06 and 1.38 (2 × s, 2 × 3H), 1.19-1.30, 1.58-1.68 and 1.73-1.85 (3 × m, 10H), 2.44 (d, 1H, *J* = 11.1 Hz), 2.44-2.54 (m, 1H), 2.67 (d × d, 1H, *J* = 10.5, 10.3 Hz), 2.71 (d × d, 1H, *J* = 11.1, 3.0 Hz), 3.45 (d × d × d, 1H, *J* = 10.3, 6.8, 3.0 Hz), 5.05 (d × d, 1H, *J* = 10.5, 6.8 Hz), 6.77-6.97 and 7.16-7.28 (2 × m, 5H); 13C NMR (ref = CDCl3, 75 MHz): *δ* = 21.8, 25.0, 25.97 26.03, 26.3, 28.9, 29.4, 46.4, 55.7, 61.8, 63.2, 77.1, 115.4, 121.5, 129.5, 158.0, 209.9; IR (ATR): *ν* = 1731 (C=O); MS (ES+): *m/z* = 302 (MH+). M.p. = 38.5 °C (column chromatography (SiO2), petroleum ether - ethyl acetate 19:1, Rf = 0.20). Yield 63%, white crystals. Anal. Calcd for C19H27NO2: C 75.71, H 9.03, N 4.65. Found: C 75.64, H 9.17, N 4.71.

* + - 1. **1-Isopropyl-3-phenoxypiperidin-4-one 4e**

1H NMR (CDCl3, 300 MHz): *δ* = 1.09 (d, 6H, *J* = 6.5 Hz), 2.52-2.70 and 3.06-3.13 (2 × m, 4H and 1H), 3.00 (septet, 1H, *J* = 6.5 Hz), 3.42 (d × d × d, 1H, *J* = 10.8, 6.3, 2.9 Hz), 4.83 (d × d, 1H, *J* = 10.3, 6.3 Hz), 6.85-6.91, 6.94-7.00 and 7.23-7.31 (3 × m, 2H, 1H and 2H); 13C NMR (ref = CDCl3, 75 MHz): *δ* = 18.4, 18.5, 41.0, 49.0, 53.9, 54.0, 79.2, 115.5, 121.6, 129.6, 157.7, 205.6; IR (ATR): *ν* = 1733 (C=O); MS (ES+): *m/z* = 234 (MH+). Column chromatography (SiO2), petroleum ether - ethyl acetate 1:1, Rf = 0.10. Yield 43%, colourless oil. HRMS (ESI) calcd for C14H20NO2 234.1494 [M + H]+, found 234.1496.

* + - 1. **3-Benzyloxy-1-isopropylpiperidin-4-one 4f**

1H NMR (CDCl3, 300 MHz): *δ* = 1.00 (d, 6H, *J* = 6.6 Hz), 2.36-2.51 and 2.82-2.98 (2 × m, 4H and 2H), 3.19 (d × d × d, 1H, *J* = 10.7, 6.3, 2.8 Hz), 4.00 (d × d, 1H, *J* = 10.2, 6.3 Hz), 4.49 and 4.84 (2 × d, 2 × 1H, *J* = 12.1 Hz), 7.21-7.36 (m, 5H); 13C NMR (ref = CDCl3, 75 MHz): *δ* = 18.38, 18.42, 40.9, 48.8, 54.0, 54.4, 72.4, 80.1, 127.9, 128.0, 128.5, 137.9, 208.0; IR (ATR): *ν* = 1727 (C=O); MS (ES+): *m/z* = 248 (MH+). Column chromatography (SiO2), petroleum ether - ethyl acetate 1:1, Rf = 0.06. Yield 45%, colourless oil. HRMS (ESI) calcd for C15H22NO2 248.1651 [M + H]+, found 248.1653.

* + - 1. **3-Benzyloxy-1-cyclohexylpiperidin-4-one 4g**

1H NMR (CDCl3, 300 MHz): *δ* = 1.19-1.31, 1.62-1.66 and 1.78-1.81 (3 × m, 5H, 1H and 4H), 2.40-2.64 (m, 5H), 3.03-3.09 (m, 1H), 3.29 (d × d × d, 1H, *J* = 11.0, 6.5, 2.8 Hz), 4.03 (d × d, 1H, *J* = 10.2, 6.5 Hz), 4.53 and 4.87 (2 × d, 2 × 1H, *J* = 12.1 Hz), 7.27-7.39 (m, 5H); 13C NMR (ref = CDCl3, 75 MHz): *δ* = 26.0, 26.2, 29.0, 29.1, 41.0, 49.2, 54.9, 62.9, 72.2, 80.2, 127.7, 127.8, 128.4, 138.0, 207.6; IR (ATR): *ν* = 1727 (C=O); MS (ES+): *m/z* = 288 (MH+). Column chromatography (SiO2), petroleum ether - ethyl acetate 4:1, Rf = 0.04. Yield 48%, colourless oil. HRMS (ESI) calcd for C18H26NO2 288.1964 [M + H]+, found 288.1965.

* + 1. **Synthesis of *cis*-4-hydroxypiperidines 5**

General procedure: To an ice-cooled solution of piperidin-4-one **4** (10 mmol) in methanol (40 mL) was added NaBH4 (20 mmol, 2 equiv) in small portions, and the mixture was heated under reflux for 2 h. Afterward, water (40 mL) was added, and the resulting mixture was extracted 3 times with 30 mL of CH2Cl2. Drying (MgSO4), filtration of the drying agent, and removal of the solvent afforded *cis*-4-hydroxypiperidines **5**. The spectral data of *cis*-4-hydroxypiperidines **5** were judged to be identical to those reported in the literature.14,16

* + 1. **Synthesis of (4*S*)-3-benzyloxy-4-hydroxy-1-isopropylpiperidines 6 and 7**

3-Benzyloxy-1-isopropylpiperidin-4-one **4f** (250 mg, 50 mM), NADH (71 mg, 5 mM), isopropylalcohol (1 mL) and an *S*-specific alcohol dehydrogenase20 (100 mg) were dissolved in MES-buffer (19 mL, 50 mM, pH 6.5). The mixture was incubated overnight in a thermoshaker (Eppendorf) at 300 rpm and 30 °C, yielding (3*S*,4*S*)-3-benzyloxy-4-hydroxy-1-isopropylpiperidine **6** and (3*R*,4*S*)-3-benzyloxy-4-hydroxy-1-isopropylpiperidine **7** in quantitative yield (ratio 1/1, based on 1H NMR).

* + - 1. **(3*S*,4*S*)-3-Benzyloxy-4-hydroxy-1-isopropylpiperidine 6**

1H NMR (CDCl3, 300 MHz): *δ* = 1.03 (d, 6H, *J* = 6.1 Hz), 1.59 (d × d × d × d, 1H, *J* = 17.2, 11.2, 5.9, 3.6 Hz), 1.94-2.05 (m, 2H), 2.20 (d × d, 1H, *J* = 11.2, 10.7 Hz), 2.74-2.85 (m, 2H), 3.11 (d, 1H, *J* = 11.0 Hz), 3.35-3.49 (m, 2H), 4.56 and 4.70 (2 × d, 2 × 1H, *J* = 11.6 Hz), 7.30-7.37 (m, 5H); 13C NMR (ref = CDCl3, 75 MHz): *δ* = 18.2, 18.4, 31.5, 46.6, 50.8, 54.4, 72.0, 73.2, 81.5, 127.9, 128.6, 138.5; IR (ATR): *ν* = 3445 (OH); MS (ES+): *m/z* = 250 (MH+). [α]D = +27.7° (*c* = 1.01, CH2Cl2). *ee* = 98.8%. Column chromatography (SiO2), petroleum ether - ethyl acetate 1:3, Rf = 0.04. Yield 45%, colourless oil. HRMS (ESI) calcd for C15H24NO2 250.1807 [M + H]+, found 250.1812.

**4.2.3.2. (3*R*,4*S*)-3-Benzyloxy-4-hydroxy-1-isopropylpiperidine 7**

[α]D = +7.6° (*c* = 0.95, CHCl3). *ee* = 98.8%. The spectral data of (3*R*,4*S*)-3-benzyloxy-4-hydroxy-1-isopropylpiperidine **7** were judged to be identical to those for *cis*-3-benzyloxy-4-hydroxy-1-isopropylpiperidine **5**.16

* + 1. **Synthesis of (4*R*)-3-benzyloxy-4-hydroxy-1-isopropylpiperidines 8 and 9**

The synthesis of (4*R*)-3-benzyloxy-4-hydroxy-1-isopropylpiperidines **8** and **9** was analogous to the synthesis of (4*S*)-3-benzyloxy-4-hydroxy-1-isopropylpiperidines **6** and **7** usingan *R*-specific alcohol dehydrogenase,21 yielding (3*S*,4*R*)-3-benzyloxy-4-hydroxy-1-isopropylpiperidine **8** and (3*R*,4*R*)-3-benzyloxy-4-hydroxy-1-isopropylpiperidine **9** in quantitative yield (ratio 1/1, based on 1H NMR).

* + - 1. **(3*S*,4*R*)-3-Benzyloxy-4-hydroxy-1-isopropylpiperidine 8**

(49%) Colourless oil. [α]D = -7.6° (*c* = 0.98, CHCl3). *ee* = 96.2%. The spectral data of (3*S*,4*R*)-3-benzyloxy-4-hydroxy-1-isopropylpiperidine **8** were judged to be identical to those for *cis*-3-benzyloxy-4-hydroxy-1-isopropylpiperidine **5**.16

**4.2.4.2. (3*R*,4*R*)-3-Benzyloxy-4-hydroxy-1-isopropylpiperidine 9**

[α]D = -27.7° (*c* = 0.97, CH2Cl2). *ee* = 95.8%. The spectral data of (3*R*,4*R*)-3-benzyloxy-4-hydroxy-1-isopropylpiperidine **9** were judged to be identical to those for (3*S*,4*S*)-3-benzyloxy-4-hydroxy-1-isopropylpiperidine **6**.

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