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4-Piperidones from Enantiomerically Pure Enones. Synthesis of 6-Alkylsubstituted 4-Oxo-pipecolic Acid Derivatives

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Abstract. The cyclization of the enantiomerically pure α,β-unsaturated ketone **1**, an aliphatic aldehyde **3** and ammonia or benzylamine gives diastereoselectively *cis*-piperidones **4/4'**. Although only modest yields were obtained, the presented cyclization has the advantage of being a single step reaction. The products **4** can serve as precursors for all-*cis*-4-hydroxy-piperidones **5** and novel pipecolic acid derivatives **9**.

The piperidine ring is part of many biologically active substances. In particular, a large number of piperidine alkaloids of great structure variety are known [1].

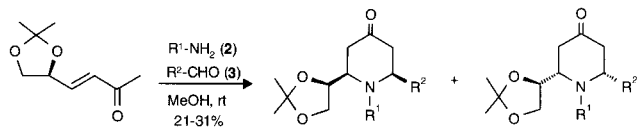
Structures of piperidine alkaloids include 4-oxo [2] and 4-hydroxy [3] derivatives as well as 2,6-disubstituted systems. For example, 2,6-disubstituted 4-hydroxy-piperidines were recently found in skin extracts of dendrobatid frogs [4].

Furthermore, (*S*)-piperidine-2-carboxylic acid (pipecolic acid) represents a natural occurring amino acid found in a variety of biologically important products [5]. Because of these aspects the synthesis of enantiomerically pure piperidine building blocks is receiving considerable attention [3, 5, 6].

There are several methods to assemble the piperidine skeleton [6, 7]. However, only a few examples are known for a three component reaction of an α,β-unsaturated ketone, an aldehyde and an amine, affording piperidin-4-ones [8]. The asymmetric version as well as the use of (*Z*)-configured enones in this cyclization reaction has not been reported so far. Therefore, we examined the reaction of the enantiomerically pure enones (*E*)- and (*Z*)-**1**, bearing a stereogenic center in γ-position, with ammonia or benzylamine **2** and an aldehyde **3** [9]. In this paper, we report on findings concerning this reaction and the conversion of the obtained piperidones into piperidinol derivatives. Furthermore, we were intrigued by the possibility to transform the chiral dioxolane moiety of **1** into a carboxylic acid function to afford novel pipecolic acid derivatives.

Results and Discussion

Scheme 1 summarizes the experimental results of the one-step reaction of (*E*)- and (*Z*)-enone **1**, ammonia or benzylamine **2** and an aldehyde **3** forming the piperidones **4** and **4'**.



1 4a-e 4'a-e

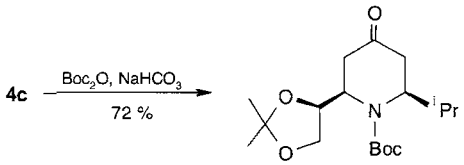
Entry		R^1	R^2	piperidone	yield(%)	4:4'
1	**(*E*)-1**	H	Me	**4a/4'a**	21	76:24
2	**(*E*)-1**	H	Et	**4b/4'b**	26	77:23
3	**(*E*)-1**	H	*i*Pr	**4c/4'c**	31	80:20
4	**(*Z*)-1**				27	66:34
5	**(*E*)-1**	H	*t*Bu	**4d/4'd**	31	67:33
6	**(*E*)-1**	Bn	*i*Pr	**4e/4'e**	27	83:17
7	**(*E*)-1** [a]				38	84:16

[a] reaction of **(*E*)-1** with the independently prepared isobutylidenebenzylimine

Scheme 1 Preparation of Piperidone Derivatives **4/4'**

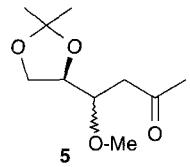
It turned out that the reaction proceeds with acceptable stereoselectivity. Only two out of four possible piperidones **4/4'** were detected by NMR spectroscopy. In all cases the major diastereomers **4a**–**4e** and for **4d** also the minor isomer **4'd** were isolated as pure compounds by chromatography.

An additional *N*-Boc derivative **4f** was prepared from **4c** according to standard procedures.



4f

The modest yields of the three component reaction were already reported by Daly *et al.* for the racemic series [8]. As one of the side-products the Michael adduct **5** was isolated, resulting from the addition of the solvent methanol to enone **1** (6–28%, 1:1 diastereomeric mixture). Similar to Daly we tried to improve the yields by changing the reaction conditions. However, all solvent (acetonitrile, chloroform, nitromethane, THF, dioxane, DMF and DMSO) and temperature variations did not result in any improvement. A two-fold excess of amine and aldehyde proved to give the best results. Further excess of amine **2** and/or aldehyde **3** did not influence the yield significantly. Efforts to extend this procedure to aromatic amines **2** (R = aryl) resulted in the exclusive formation of Michael adduct **5**. Adduct **5** was found as sole product when the reaction was performed under high pressure (10 kbar).



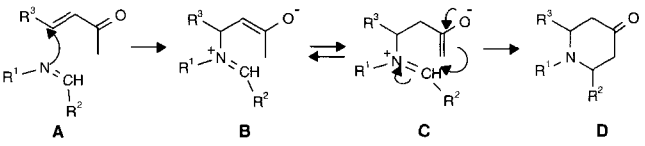
5

Concerning the mechanism Daly *et al.* supposed the primary formation of an imine from aldehyde and amine, followed by a Michael-type reaction with the enone system (formation of B in Scheme 2) and subsequent intramolecular Mannich cyclization of the adduct (see intermediat C in Scheme 2). The reaction of α,β-unsaturated ketones with imines affording 4-piperidones has been already been described for some cases [10]. Alternatively, an initial Mannich reaction of the imine followed by an aza-Michael reaction has to be considered.

To get more insight into the course of the reaction, the preformed isobutylidenebenzylamine was reacted with enone **1** (Scheme 1, entry 7). Indeed, the piperidones **4e/4'e** were found with the same diastereomeric ratio as in the three-component reaction.

On the other hand, the benzylamine alone adds to the C–C double bond of the unsaturated ketone **1** under the same conditions without stereoselectivity [9].

The determination of the stereochemical outcome of the three component reaction is based on X-ray analysis of major isomer **4d** (Fig. 1), which unambiguously proved the *cis*-arrangement of the substituents in position 2 and 6 as was assigned by Edwards for the racemic series on the basis of IR-investigations [8]. In addition, the relative orientation of the H-atoms at the stereogenic centre in the side chain and at the neighbouring ring C atom is *syn*. This finding is in accordance with the known addition of amines to γ-chiral-α,β-unsaturated carbonyl compounds [11].



Scheme 2 Proposed Mechanism for the Formation of Piperidones **4/4'**

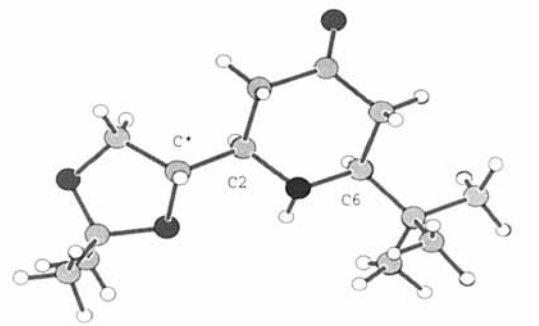


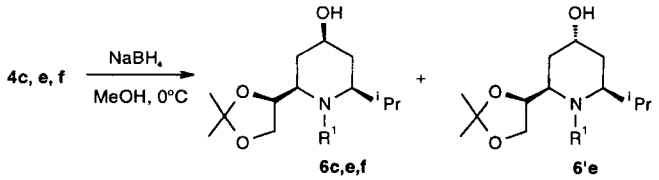
Fig. 1 X-ray Analysis of Compound **4d**

^{1}H NMR-investigations, including NOE-experiments, established the 2,6-di-equatorial *cis*-substitution for all major diastereomers **4a–d** and also for the minor diastereomer **4d'**, i.e. unlike in Daly's investigations no *trans*-product could be detected [12].

In the course of our further investigations the piperidones **4c** and **4e** were reduced with $NaBH_4$. Interestingly, derivative **4c** (R^1 = H) exclusively afforded diastereomer **6c,** whereas reduction of **4e** (R^1 = Bn) and **4f** (R^1 = Boc) led to a mixture of diastereomers **6/6'**. For **4c** the use of the less chelating $NaBH(OMe)_3$ gave also rise to the highly diastereoselective formation of **6c** (Scheme 3).

The configuration of the newly created stereocenter at C4 was established by analysis of a 600 MHz-^{1}H NMR spectrum of compound **6c**. The large coupling constants of 11.5 Hz clearly indicate the 1,2-diaxial proton interactions of H-4 and H-3_{axial} as well as H-4 and H-5_{axial}.

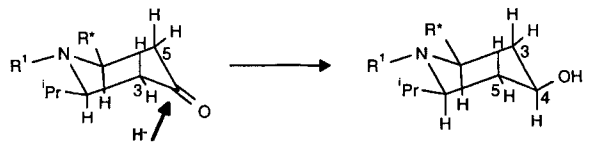
This fact suggests an axial attack of the hydride ion upon the carbonyl group. In the most stable conformation of **4** the substituents in position 2 and 6 are placed in an equatorial position. The observed preference of isomer **6** is now attributed to an easier approach of the



cond.	R^1	products	yield (%)	6 : 6'
$NaBH_4$	H	**6c**	86	> 95 : 5
$NaBH(OMe)_3$	H	**6c**	81	> 95 : 5
$NaBH_4$	Bn	**6e/6'e**	95	72 : 28
$NaBH_4$	Boc	**6f**	89	90 : 10

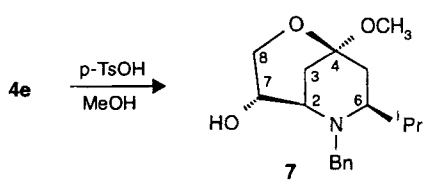
Scheme 3 2,6-Disubstituted 4-Hydroxy-piperidines **6/6'**

hydride to the carbonyl group from the axial side. In particular, the equatorial attack is hindered by repulsive interactions with the axial hydrogens H-3_{axial} and H-5_{axial} [7, 13].

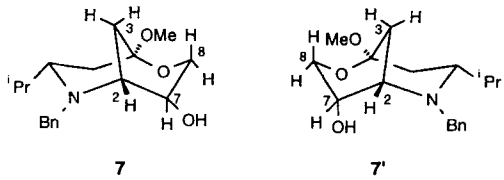


In **4e** (R^1 = Bn) and **4f** (R^1= Boc) the N-substituents are likely to destabilize the chair-like conformation of the piperidon resulting in a lower barrier for the equatorial attack [7, 13].

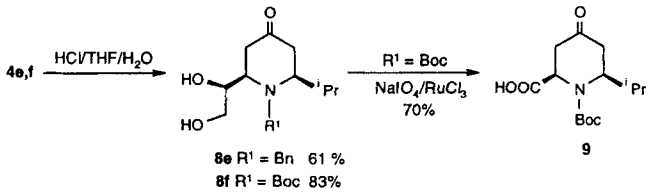
As mentioned above, another aim of our investigations was to transform piperidones **4/4'** into pipecolic acid derivatives. This approach was based on the idea of converting the dioxolane moiety into a carboxylic acid function after it had served as the chiral controller in the asymmetric cyclization step. The removal of the protecting isopropylidene group was attempted by treatment of **4e** with *p*-TsOH in methanol. The spectroscopic data, however, revealed that the bicyclic system **7** was formed rather than the deprotected diol **8e**. Obviously, the primary liberated OH-group attacks the carbonyl C-atom affording the acetal **7** in 48% yield by incorporating one molecule of MeOH.



This bicyclic product **7** offered the chance to get evidence for the designated stereochemistry at C2/C6, and the relative configuration at C2/C7 of the precursor piperidone **4e** by means of NMR-techniques. C-H-COSY and H-H-COSY experiments allowed the unequivocal assignment of chemical shifts and coupling constants. NOE-experiments between H3/H8 and H3/H2 served as proof of the conformational arrangement. The differentiation between structure **7** and the alternative compound **7'** (derived from **4'e**) succeeded by analysis of coupling constants according to the Karplus equation. For the protons at C2 and C7 in **7'** a coupling constant of about 10 Hz is expected due to the dihedral angle of about 0°. However, no coupling constant was found for H2/H7 thus proving their 90° arrangement as in **7**.



Further variation of the reaction conditions revealed that the isopropylidene moiety could be removed by performing the reaction in the system HCl/THF/H_2O to afford diols **8e** and **8f** in good yields. However, all attempts to oxidize compound **8e** with $NaIO_4/RuCl_3$ gave only complex mixtures. This result may be caused by the electron donating properties of the ring-N-atom in **8e**. On the other hand the *N*-Boc derivative **8f** could be transformed into the novel 4-oxo-pipecolic acid **9**. Compound **9** was fully characterized by spectroscopic methods and elemental analysis. Chiral HPLC-investigations confirmed the enantiopurity of **9** (*e.e.* >98%).



The continuous support of our work by Prof. J. Liebscher, Humboldt-Universität zu Berlin is gratefully acknowledged.

Experimental

The ^1H NMR spectra were recorded on a Bruker AC-300 (300 MHz) and AC-600 (600 MHz) spectrometer, the ^{13}C NMR spectra on a Bruker AC-300 (75 MHz) spectrometer. The samples were dissolved in $CDCl_3$ with tetramethylsilane (TMS) as internal standard *J* in Hz. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad singlet. Elemental analysis were performed in a Leco CHNS-932 apparatus. Optical rotations were measured on a Perkin Elmer 241 polarimeter using a 2 ml cell (c = 1.0; CH_2Cl_2). The reactions and the purity of compounds were monitored by TLC performed on pre-coated silica gel plates with a fluorescence indicator (Merck 60 F_{254}). Column chromatography was carried out on Merck Kieselgel 60 (0.040–0.063 µm). HPLC analyses were carried out on a Knauer instrument with a Chiralcel ODR column, detection at 220 nm and Chiralyser software; eluent 0.5N $HClO_4$ in $NaClO_4$-solution/MeCN = 60 : 40, flow rate 0.8 ml/min.

The diastereomeric ratios have been determined from the intensities of three characteristic signals in the ^{13}C-NMR spectra from the crude reaction mixture.

Enone **1** was synthesized according to the literature procedure [14].

2,6-Disubstituted Piperidones (4) and (4') (General Procedure)

NH_4OAc (12 mmol, 1 g) or benzylamine (10 mmol, 1.07 g) and acetic acid (10 mmol, 600 mg) were added to enone **1** (5 mmol, 850 mg) in 5 mL of methanol. The mixture was cooled to 0 °C and aldehyde **3** (10 mmol) was added. The reaction mixture was stirred for 2 days at r.t., dissolved in ether (25 mL) and washed with saturated K_2CO_3-solution. The aqueous phase was extracted with ether and the combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane–EtOAc = 7 : 3).

(2R, 6R)-2-[(4S)-2,2-Dimethyl-[1,3]dioxolane-4-yl]-6-methyl-piperidine-4-one (**4a**)

yellowish oil, yield 21%, $[\alpha]_{546}^{20}$ = +5.5° (*c* 1.0 in CH_2Cl_2), R_f = 0.1 (hexane–EtOAc = 1:1). – ^{13}C NMR δ/ppm = 207.9 (C=O), 109.6 (OCO), 78.9 (CH-O), 66.3 (CH_2O), 59.1 (C2), 51.6 (C6), 49.9 (C3), 43.8 (C5), 26.7 and 25.4 ($\underline{C}H_3C$), 22.5 (6-CH_3). – ^{1}H NMR δ/ppm = 3.93–4.01 (m, 2H, CH_2O), 3.61–3.68 (m, 1H, CH-O), 2.96 (ddd, 1H, *J* = 2.8/5.8/11.6, H6), 2.86 (q, 1H, *J* = 7.3, H2), 2.04–2.34 (m, 5H, H3, H5, NH), 1.38 and 1.33 (s, 3H, CH_3C), 1.19 (dd, 3H, *J* = 1.4/6.2, 6-CH_3).

$C_{11}H_{19}NO_3$	calcd.:	C 61.94	H 8.98	N 6.56
(213.28)	found:	C 62.05	H 8.96	N 6.69.

(2R, 6R)-2-[(4S)-2,2-Dimethyl-[1,3]dioxolane-4-yl]-6-ethyl-piperidine-4-one (**4b**)

yellowish oil, yield 26% $[\alpha]_{546}^{20}$ = +2.0° (*c* 1.0 in CH_2Cl_2), R_f = 0.2 (hexane – EtOAc = 1:1). – ^{13}C NMR δ/ppm = 208.0 (C=O), 109.5 (OCO), 78.8 (CH-O), 66.2 (CH_2O), 59.0, 57.5 (C6, C2), 47.7 (C3), 44.1 (C5), 29.6 (6-CH_2), 26.7 and 25.3 ($\underline{C}H_3C$), 9.9 (CH_2–$\underline{C}H_3$). – ^{1}H NMR δ/ppm = 3.86–3.98 (m, 2H, CH_2O), 3.63 (ddd, 1H, *J* = 6.1/7.6/8.8, CH-O), 3.18 (b, 1H, NH), 2.81 (q, 1H, *J* = 6.1 , H2), 2.69 (ddd, 1H, *J* = 2.7/6.3/11.7, H6), 2.34 (dd, 1H, *J* = 1.3/13.9, H3), 2.08–2.13 (m, 2H, H5), 2.00 (dd, 1H, *J* = 14.0/11.5, H3), 1.50 (dq, 2H, *J* = 6.5/13.7, 6-CH_2), 1.35 and 1.29 (s, 3H, CH_3C), 0.86–0.92 (m, 3H, CH_2–$\underline{C}H_3$).

$C_{12}H_{21}NO_3$	calcd.:	C 63.40	H 9.31	N 6.16
(227.30)	found:	C 63.85	H 9.51	N 6.12.

(2R, 6S)-2-[(4S)-2,2-Dimethyl-[1,3]dioxolane-4-yl]-6-isopropyl-piperidine-4-one (**4c**)

yellowish oil, yield 31% (from (***E***)-**1**), 27% (from (***Z***)-**1**), $[\alpha]_{546}^{20}$ = +7.0° (*c* 1.0 in CH_2Cl_2), R_f = 0.4 (hexane–EtOAc = 1:1). – ^{13}C NMR δ/ppm = 208.9 (C=O), 109.5 (OCO), 78.8 (CH-O), 66.2 (CH_2O), 61.6 (C2), 58.9 (C6), 45.1, 44.5 (C3, C5), 33.0 ($\underline{C}HMe_2$), 26.7 and 25.4 ($\underline{C}H_3C$), 18.7 and 18.0 ($\underline{C}H_3$–CH). – ^{1}H NMR δ/ppm = 3.91–4.00 (m, 2H, CH_2O), 3.68 (ddd, 1H, *J* = 6.5/6.0/7.6, CH-O), 2.78 (q, 1H, *J* = 6.8, H2), 2.56 (ddd, 1H, *J* = 3.3/6.1/11.8, H6), 2.32 (dd, 1H, *J* = 2.3/14.0, H3), 2.10–2.13 (m, 3H, H5, NH), 2.05 (dd, 1H, *J* = 13.7/11.8, H3), 1.68 (o, *J* = 6.6 , $C\underline{H}Me_2$), 1.36 and 1.31 (s, 3H, CH_3C), 0.92 and 0.90 (d, 3H, 6.8, $\underline{C}H_3$–CH).

$C_{13}H_{23}NO_3$	calcd.:	C 64.69	H 9.61	N 5.81
(241.33)	found:	C 64.40	H 9.82	N 5.23.

(2R, 6S)-6-tert-Butoxycarbonyl-2-[(4S)-2,2-dimethyl-[1,3]dioxolane-4-yl]-piperidine-4-one (**4d**)

colorless crystals, yield 31%, *m.p.* 88 °C, $[\alpha]_{546}^{20}$ = +3.0° (*c* 1.0 in CH_2Cl_2), R_f = 0.5 (hexane – EtOAc = 1:1). – ^{13}C NMR δ/ppm = 209.7 (C=O), 109.4 (OCO), 78.7 (CH-O), 66.2 (CH_2O), 65.1 (C2), 58.8 (C6), 45.1, 44.7 (C3, C5), 33.6 ($\underline{C}(CH_3)_3$), 26.1 ($C(\underline{C}H_3)_3$), 26.7 and 25.4 ($\underline{C}H_3C$). – ^{1}H NMR δ/ppm = 3.94–4.00 (m, 2H, CH_2O), 3.67–3.77 (m, 1H, CH-O), 3.13 (b, 1H, NH), 2.72 (q, 1H, *J* = 6.3, H6), 2.44 (dd, 1H, *J* = 2.7/12.0, H2), 2.32 (dd, 1H, *J* = 1.8/13.8, H3), 2.10–2.14 (m, 2H, H5), 2.04 (dd, 1H, *J* = 13.5/16.8, H3), 1.35 and 1.30 (s, 3H, CH_3C), 0.89 (s, 9H, $\underline{C}H_3$-C).

$C_{14}H_{25}NO_3$	calcd.:	C 65.84	H 9.86	N 5.48
(255.36)	found:	C 65.93	H 9.48	N 5.58.

Crystal Structure Analysis of Compound (4d)

$C_{14}H_{25}NO_3$, $P2_12_12_1$, *a* = 6.0572 (15), *b* = 9.6754 (13), *c* = 25.666 (4) Å, *Z* = 4, *T* = 295 K, colorless crystals, 0.76 × 0.48 × 0.19 mm, Mo–K_α radiation, STADI-4 Diffraktometer, $2\Theta_{max}$ 55°. Refinement on F^2, (programm SHELXL-93, G. M. Sheldrick, Univ. of Göttingen). Final $wR(F^2)$ = 0.098, conventionell *R(F)* 0.042, for 249 parameters. The absolute configuration could not be determined directly but was based on the known configuration of the starting material [15].

(2S, 6R)-6-tert-Butoxycarbonyl-2-[(4S)-2,2-dimethyl-[1,3]dioxolane-4-yl]-piperidine-4-one (**4d'**) *(minor diastereomer)*

colorless oil, yield 10%, $[\alpha]_{546}^{20}$ = 30.1° (*c* 1.0 in CH_2Cl_2), R_f = 0.6 (hexane – EtOAc = 1:1). – ^{13}C NMR δ/ppm = 210.0 (C=O), 109.3 (OCO), 78.2 (CH-O), 65.3 (CH_2O), 65.0 (C2), 57.3 (C6), 50.1 (CH_2N), 44.0, 43.9 (C3, C5), 33.7 ($\underline{C}(CH_3)_3$), 26.1 ($C(\underline{C}H_3)_3$), 26.4 and 25.1 ($\underline{C}H_3C$). – ^{1}H NMR δ/ppm = 4.02–4.07 (m, 2H, CH_2O), 3.94–3.96 (m, 1H, CH-O), 2.93 (ddd, 1H, *J* = 3.0/4.0/12.2, H2), 2.45 (dd, 1H, *J* = 2.7/11.9, H6), 2.27–2.36 (m, 4H, H3, H5), 1.69 (b, 1H, NH), 1.37 and 1.30 (s, 3H, CH_3C), 0.86 (s, 9H, $(\underline{C}H_3)_3C$).

$C_{14}H_{25}NO_3$	calcd.:	C 65.84	H 9.86	N 5.48
(255.36)	found:	C 65.80	H 9.83	N 5.59.

(2R, 6S)-1-Benzyl-2-[(4S)-2,2-dimethyl-[1,3]dioxolane-4-yl]-6-isopropyl-piperidin-4-one (**4e**)

yellowish oil, yield 27%, $[\alpha]_{546}^{20}$ = +38.0° (*c* 1.0 in CH_2Cl_2), R_f = 0.5 (hexane – EtOAc = 8:2). – ^{13}C NMR δ/ppm = 209.4 (C=O), 139.0 (ar. C), 128.5, 127.3 (ar. CH), 109.6 (OCO), 77.1 (CH-O), 67.9 (CH_2O), 63.9, 58.5 (C2, C6), 39.6, 37.8 (C3, C5), 29.6 ($\underline{C}H(Me)_2$), 26.3 and 25.5 ($\underline{C}H_3C$), 20.2 and 20.1 ($\underline{C}H_3$–CH). – ^{1}H NMR δ/ppm = 7.18–7.28 (m, 5H, ar. CH), 4.11 (q, 1H, CH-O), 3.93 (AB, 1H, *J* = 13.9, CH_2N), 3.68–3.87 (m, 2H, CH_2O), 3.53 (AB, 1H, *J* = 14.0, CH_2N), 2.96 (q, 1H, *J* = 5.9, H2), 2.65 (ddd, 1H, *J* = 6.5/8.0/12.4, H6), 2.40–2.52 (m, 3H, H3, H5), 2.24 (dd, 1H, *J* = 8.0/14.7, H3), 1.72 (o, 1H, *J* = 6.5, $C\underline{H}Me_2$), 1.20 and 1.19 (s, 3H, CH_3C), 0.95 and 0.81 (d, 3H, *J* = 6.5, $\underline{C}H_3$–CH).

$C_{20}H_{29}NO_3$	calcd.:	C 72.47	H 8.82	N 4.23
(331.45)	found:	C 71.69	H 9.27	N 3.79.

(2R, 6S)-1-tert-Butoxycarbonyl-2-[(4S)-2,2-dimethyl-[1,3]dioxolane-4-yl]-6-isopropyl-piperidine-4-one (**4f**)

Boc_2O (4.8 mmol, 960 mg) and an aqueous suspension of $NaHCO_3$ (2.65 g in 10 mL water) were added to a solution of piperidone **4c** (400 mg, 1.66 mmol) in 10 mL dioxane. After stirring the mixture overnight, the solvent was removed under reduced pressure and the residue dissolved in 25 mL ether. The solution was washed with H_2O and dried (Na_2SO_4). After removal of the solvent the residue was purified by column chromatography (SiO_2, hexane – EtOAc = 7 : 3), to afford the pure *N*-Boc-piperidone **4f** (408 mg, 72%) and unreacted starting material **4c** (72 mg, 18%). – colorless oil, $[\alpha]_{546}^{20}$ = –76.8° (*c* 1.0 in CH_2Cl_2), R_f = 0.5 (hexane – EtOAc = 7:3). – ^{13}C NMR δ/ppm = 207.8 (C4), 155.6 (NCOO), 109.9 (OCO), 80.5 (<u>C</u>(CH_3)$_3$), 77.0 (CH-O), 67.3 (CH_2O), 58.9 (C2), 54.3 (C6), 42.1, 40.6 (C3, C5), 32.9 (<u>CH</u>(CH_3)$_2$), 28.2 (C(<u>CH_3</u>)$_3$), 26.5 and 25.2 (<u>CH_3</u>C), 20.2 and 20.0 (<u>CH_3</u>–CH). – ^{1}H NMR δ/ppm = 4.71 (td, 1H, *J* = 8.2/3.6, H2), 4.26 (m, 1H, H6), 4.11 (q, 1H, *J* = 7.3, CH-O), 3.96 (ddd, 1H, *J* = 1.0/6.0/8.0, CH_2O), 3.48 (t, 1H, *J* = 7.5, CH_2O), 2.62 (dd, 1H, *J* = 15.6/8.2, H3), 2.50 (m, 2H, H5), 2.09 (dd, 1H, *J* = 3.4/15.7, H3), 1.76 (o, 1H, *J* = 6.6, C<u>H</u>Me_2), 1.41 (s, 9H, C(CH_3)$_3$), 1.36 and 1.23 (s, 3H, CH_3C), 0.97 and 0.86 (d, 3H, 6.6, <u>CH_3</u>–CH).

$C_{18}H_{31}NO_5$	calcd.:	C 63.32	H 9.15	N 4.10
(341.45)	found:	C 63.28	H 9.25	N 4.57.

4-Hydroxy-piperidines (6) and (6') (General Procedure)

$NaBH_4$ (22 mg, 0.6 mmol) or $Na(OMe)_3BH$ (76 mg, 0.6 mmol) was added at 0 °C to a solution of piperidone **4** (0.25 mmol) in 3 mL methanol. After stirring for 2h at 0 °C water (25mL) was added. The solution was extracted with CH_2Cl_2 three times. The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography of the residue (SiO_2, $CHCl_3$/MeOH = 85:15) yielded the pure 4-hydroxy-piperidines **6/6'**.

(2R, 4S, 6S)-2-[(4S)-2,2-Dimethyl-[1,3]dioxolane-4-yl]-6-isopropyl-piperidine-4-ol (**6c**)

colorless oil, yield 86%, $[\alpha]_{546}^{20}$ = 6.0 (*c* 1.0 in CH_2Cl_2), R_f = 0.3 ($CHCl_3$/MeOH = 85:15). – ^{13}C NMR δ/ppm = 109.2 (OCO), 79.3 (CH-O), 69.2 (C4), 66.6 (CH_2O), 60.1, 58.0 (C2, C6), 38.2, 37.5 (C3, C5), 32.8 (<u>CH</u>$(Me)_2$), 26.8 and 25.5 (<u>CH_3</u>C), 19.2 and 18.6 (<u>CH_3</u>–CH). – ^{1}H NMR (600 MHz) δ/ppm = 3.95–4.00 (m, 2H, CH_2O), 3.59–3.67 (m, 2H, CH-O, H4), 3.20 (b, 2H, OH, NH), 2.56 (td, 1H, *J* = 8.0/2.5, H2), 2.29 (ddd, 1H, *J* = 1.8/6.4/11.2, H6), 1.97 (dt, 1H, *J* = 2.2/11.9, H3), 1.70 (dt, 1H, *J* = 2.0/11.7, H5), 1.64 (o, 1H, *J* = 6.7, C<u>H</u>Me_2), 1.37 and 1.32 (s, 3H, CH_3C), 1.12 (q, 1H, H3), 1.09 (q, 1H, *J* = 11.5, H5), 0.94 and 0.91 (d, 3H, *J* = 6.8, <u>CH_3</u>–CH).

$C_{18}H_{31}NO_5$	calcd.:	C 64.16	H 10.35	N 5.76
(243.34)	found:	C 64.17	H 9.89	N 5.77.

(2R, 4S, 6S)-1-Benzyl-2-[(4S)-2,2-dimethyl-[1,3]dioxolane-4-yl]-6-isopropyl-piperidine-4-ol (**6e**) and *(2R, 4R, 6S)-1-Benzyl-2-[(4S)-2,2-dimethyl-[1,3]dioxolane-4-yl]-6-isopropyl-piperidine-4-ol* (**6'e**)

yellowish oil, **6e**: yield 95%, R_f = 0.25 (hexane–EtOAc = 7:3). – ^{13}C NMR δ/ppm = 139.8 (ar.C), 128.8, 128.3, 127.0 (ar. CH), 109.0 (OCO), 75.1 (CH-O), 68.8 (CH_2O), 67.1 (C4), 62.1, 57.8 (C2, C6), 48.7 (CH_2N), 31.2, 28.2 (C3, C5), 29.4 (<u>CH</u>$(Me)_2$), 26.5 and 26.1 (<u>CH_3</u>C), 20.9 and 20.5 (<u>CH_3</u>–CH). – ^{1}H NMR δ/ppm = 7.19–7.25 (m, 5H, ar. CH), 4.10–4.24 (m, 2H, CH_2O), 3.86–3.97 (m, 2H, CH-O, H4), 3.68 and 3.42 (AB, 1H, *J* = 14.0, CH_2N), 2.59–2.71 (m, 1H, H2), 2.18–2.30 (m, 1H, H6), 1.41–2.00 (m, 6H, H3, H5, C<u>H</u>Me_2, OH), 1.25 and 1.23 (s, 3H, CH_3C), 0.99 and 0.88 (d, 3H, *J* = 6.4, <u>CH_3</u>–CH). **6'e**: – ^{13}C NMR δ/ppm = 140.3 (ar.C), 128.5, 128.1, 126.9 (ar. CH), 109.2 (OCO), 74.9 (CH-O), 68.4 (CH_2O), 66.1 (C4), 62.0, 56.3 (C2, C6), 50.8 (CH_2N), 31.2, 28.4 (C3, C5), 29.7 (<u>CH</u>$(Me)_2$), 26.7 and 25.6 (<u>CH_3</u>C), 20.7 and 20.6 (<u>CH_3</u>–CH).

(2R, 4S, 6S)-1-tert-Butoxycarbonyl-2-[(4S)-2,2-dimethyl-[1,3]dioxolane-4-yl]-6-isopropyl-piperidine-4-ol (**6f**)

colourless crystals, yield 89%, *m.p.* 137–138 °C, $[\alpha]_{546}^{20}$ = 35.3° (*c* 1.0 in CH_2Cl_2), R_f = 0.45 (hexan–AcOEt = 7:3). – ^{13}C NMR δ/ppm = 156.3 (C=O), 109.1 (OCO), 79.6 (CMe_3), 78.4 (CH-O), 67.5 (CH_2O), 64.4 (C–OH), 55.9 (C2), 51.5 (C6), 34.3 (<u>C</u>HMe_2), 33.9, 33.3 (C3, C5), 28.3 (C<u>Me</u>$_3$), 26.7 and 25.5 (<u>CH_3</u>C), 20.5 and 20.1 (CH<u>Me</u>$_2$). – ^{1}H NMR δ/ppm = 4.71 (td, 1H, *J* = 8.5/3.7, H2), 4.20 (q, 1H, *J* = 7.8/5.9, CH-O), 3.87 (dd, 1H, *J* = 5.9/7.9, CH_2O), 3.78 (m, 2H, H4, H6), 3.39 (t, 1H, *J* = 7.8, CH_2O), 1.96 (m, 1H, C<u>H</u>Me_2), 1.86 (m, 1H, H3), 1.75 (dddd, 1 H, *J* = 1.0/3.7/7.9/13.6, H5), 1.59 (ddd, 1H, *J* = 13.7/6.5/4.8, H5), 1.30 (s, 9H, C(CH_3)$_3$), 1.29 (m, 1H, H3), 1.27 and 1.17 (s, 3H, CH_3C), 0.84 and 0.79 (d, 3H, 6.6, <u>CH_3</u>–CH).

$C_{18}H_{31}NO_5$	calcd.:	C 64.16	H 10.35	N 5.76
(243.34)	found:	C 64.17	H 9.89	N 5.77.

(4S, 7S, 2R, 6S)-1-Benzyl-6-isopropyl-4-methoxy-9-oxa-1-aza-bicyclo[3.3.1]nonane-7-ol (**7**)

p-TosOH (200 mg, 1 mmol) was added to a solution of piperidone **4e** (0.33g, 1 mmol) in methanol/H_2O (10 ml, 20/1, v/v). After stirring the mixture for 18h at r.t. the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2, washed with saturated aqueous $NaHCO_3$ and dried ($MgSO_4$). Removal of the solvent and column chromatography of the residue (SiO_2, hexane–EtOAc = 1 : 1) afforded 139 mg pure compound **7** (48%). – colorless oil, $[\alpha]_{546}^{20}$ = –58.5° (*c* 1.0 in CH_2Cl_2), R_f = 0.4 (hexane–EtOAc = 1:1). – ^{13}C NMR δ/ppm = 139.5 (ar. C), 128.6, 128.4 and 126.9 (ar. CH), 109.0 (C4), 75.6 (C7), 64.8 (C8), 59.4, 59.2 (C2, C6), 53.1 (CH_2N), 49.5 (CH_3O), 35.0, 34.9 (C3, C5), 27.2 (<u>C</u>H$(Me)_2$), 19.4 and 14.4 (<u>CH_3</u>C). – ^{1}H NMR δ/ppm = 7.27–7.29 (m, 5H, ar. CH), 4.17 (t, 1H, *J* = 6.0, H7), 4.00 (AB, 1H, *J* = 14.1, CH_2N), 3.43 (dd, 1H, *J* = 11.3/6.8, H8), 3.36 (dd, 1H, *J* = 11.2/5.5, H8), 3.31 (s, 3H, CH_3O), 3.18 (AB, 1H, *J* = 14.1, CH_2N), 3.08 (d, 1H, *J* = 4.8, H2), 2.70 (dd, 1H, *J* = 5.1/10.1, H6), 2.21 (qd, 1H, *J* = 6.8/2.6, C<u>H</u>Me_2), 1.98 (ddd, 1H, *J* = 3.6/ 5.0/11.0, H3), 1.78 (ddd, 1H, *J* = 3.5/5.5/12.8, H5), 1.56 (dd, 1H, *J* = 10.8/12.7, H5), 1.35 (d, 1H, *J* = 11.0, H3), 0.92 (d, 3H, *J* = 6.8, CH_3C), 0.88 (d, 3H, *J* = 6.9, CH_3C).

$C_{18}H_{27}NO_3$	calcd.:	C 70.78	H 8.91	N 4.58
(305.42)	found:	C 70.92	H 8.59	N 4.28.

(2R, 6S)-1-Benzyl-2-[(1S)-1,2-dihydroxyethyl]-6-isopropyl-piperidine-4-one (**8e**)

Piperidone **4e** (1 mol, 331 mg) was dissolved in 10 mL of

THF/H_2O (4 : 1) and 1 mL conc. HCl was added. After stirring for 4 h at r.t., 3 ml conc. aqueous ammonia was added and the solvent was removed under reduced pressure. After addition of 2 mL aqueous NaOH (15%) the reaction mixture was extracted several times with CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and the solvent was removed on rotary evaporator. Purification by column chromatography (SiO_2, MeOH–$CHCl_3$ = 4 : 96) yielded 178 mg (61%) of diol **8e**. – ^{13}C NMR δ/ppm = 211.3 (C4), 138.6, 128.7, 71.3 (CH-O), 64.9 (CH_2O), 63.9, 59.0 (C2,C6), 49.3 (CH_2-Ph), 40.3, 37.3 (C3, C5), 30.0 ($CH(CH_3)_2$), 20.1 and 19.4 (CH_3–CH).

$C_{17}H_{25}NO_3$	calcd.:	C 70.07	H 8.65	N 4.81
(291.39)	found:	C 69.45	H 9.09	N 4.61.

(2R, 6S)-1-tert-Butoxycarbonyl-2-[(1S)-1,2-dihydroxyethyl]-6-isopropyl-piperidine-4-one (**8f**)

Piperidone **4f** (1 mmol, 341 mg) was dissolved in 10 mL of THF/H_2O (4 : 1) and 1 mL conc. HCl was added. After stirring for 4 h at r.t., 3 ml conc. aqueous ammonia werl added and the solvent was removed under reduced pressure. After addition of 2 mL aqueous NaOH (15%) the reaction mixture was extracted several times with CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and the solvent was removed on rotary evaporator. Purification by column chromatography (SiO_2, hexane–EtOAc = 1 : 1) yielded 250 mg (83%) of diol **8f**. colourless oil, $[\alpha]_{546}^{20}$ = +100.9° (*c* 1.7 in CH_2Cl_2), R_f = 0.3 (hexane – EtOAc = 1:1). – ^{13}C NMR δ/ppm = 207.9 (C4), 158.0 (NCOO), 81.7 ($C(CH_3)_3$), 76.0 (CH-O), 63.9 (CH_2O), 58.8 (C6), 53.4 (C2), 41.3, 40.3 (C3, C5), 32.2 ($CHMe_2$), 28.2 ($C(CH_3)_3$), 20.4 and 19.8 (CH_3–CH). – ^1H NMR δ/ppm = 4.63–4.66 (m, 1H, H6), 4.13–4.16 (m, 1H, H2), 3.60–3.65 (m, 2H, CH-O, CH_2O), 3.43–3.47 (m, 1H, CH_2O), 2.56–2.65 (m, 2H, H3, H5), 2.46 (dd, 1H, J = 7.0/16.4, H5), 2.42 (dd, 1H, *J* = 7.1/16.5, H3), 1.92–1.96 (m, 1H, $CHMe_2$), 1.42 (s, 9H, $C(CH_3)_3$), 0.99 and 0.85 (d, 3H, *J* = 6.5, CH_3–CH).

$C_{15}H_{27}NO_5$	calcd.:	C 59.77	H 9.03	N 4.65
(301.38)	found:	C 59.49	H 8.59	N 4.34.

(2R, 6S)-1-tert-Butoxycarbonyl-6-isopropyl-4-oxo-piperidine-2-carboxylic acid (**9**)

Diol **8f** (65 mg, 0.215 mol) was dissolved in 2 ml MeCN/CCl_4 (1 : 1). A solution of $NaIO_4$ (116 mg, 0.54 mol) in H_2O (1 mL) and 5 mg $RuCl_3$ were added. After stirring for 2 h at r.t., 10 mL of ether were added. The mixture was stirred for a further 5 min. Then the solution was cooled to 0 °C and $MgSO_4$ was added. The mixture was filtered over celite and the organic solvents were removed under reduced pressure. Purification by column chromatography (SiO_2, hexane – EtOAc = 1:1) afforded the pipecolic acid derivative **9** (43 mg, 70%). – colorless crystals, *m.p.* 117 °C, $[\alpha]_{546}^{20}$ = +179.0 (*c* 0.8 in CH_2Cl_2), R_f = 0.2 (hexane–EtOAc = 1:1). – ^{13}C NMR δ/ppm = 205.4 (C4), 176.0 (COOH), 157.0 (NCOO), 82.0 ($C(CH_3)_3$), 58.5 (C6), 54.0 (C2), 42.2, 39.0 (C3, C5), 33.5 ($CHMe_2$), 28.2 ($C(CH_3)_3$), 20.0 and 19.6 (CH_3–CH). – ^1H NMR δ/ppm = 6.95 (b, 1H, COOH), 4.64–4.80 (m, 1H, H6), 4.04–4.06 (m, 1H, H2), 2.62–2.72 (m, 3H, H3, H5), 2.48 (dd, 1H, *J* = 6.3/17.3, H3), 1.46–1.67 (m, 1H, $CHMe_2$), 1.41 (s, 9H, $C(CH_3)_3$), 1.03 und 0.84 (d, 3H, *J* = 6.3, CH_3–CH).

HPLC-investigation: t_R= 4.63 min, enantiomeric excess > 98%.

$C_{14}H_{23}NO_5$	calcd.:	C 58.93	H 8.12	N 4.91
(285.34)	found:	C 59.36	H 8.32	N 4.87.

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