

The Absolute Configuration of (+)-Ethyl *cis*-1-Benzyl-3-hydroxypiperidine-4-carboxylate and (+)-4-Ethyl 1-Methyl *cis*-3-Hydroxypiperidine-1,4-dicarboxylate; a Revision

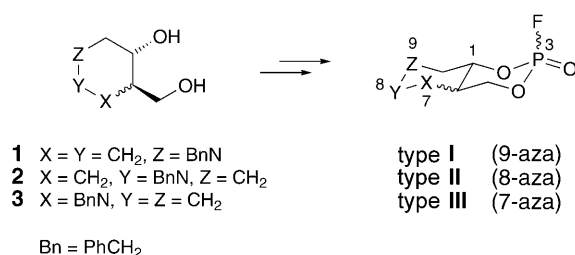
by Piergiorgio A. Lorenzetto, Andreas Strehler, and Peter Rüedi*

Organisch-chemisches Institut der Universität Zürich, Winterthurerstrasse 190, CH-8057 Zürich
(phone: 044 635 42 41)

Discrepancies between chiroptical data from the literature and our determination of the structure of the title compounds (+)-**5** and (+)-**9a** were resolved by an unambiguous assignment of their absolute configuration. Accordingly, the dextrorotatory *cis*-3-hydroxy esters have (3*R*,4*R*)- and the laevorotatory enantiomers (3*S*,4*S*)-configuration. The final evidences were demonstrated on both enantiomers (+)- and (–)-**5** by biological reduction of **4** by bakers' yeast and stereoselective [Ru^{II}(binap)]-catalyzed hydrogenations of **4** (Scheme 2), by the application of the NMR Mosher method on (+)- and (–)-**5** (Scheme 3), as well as by the transformation of (+)-**5** into a common derivative and chiroptical correlation (Scheme 4).

1. Introduction. – In the course of our studies on the irreversible inhibition of acetylcholinesterase and related serine hydrolases by organophosphates – in particular the investigation of the stereochemical course of the inhibition reaction [1] and the physiologically active conformation of acetylcholine [2] – we have prepared several 3-substituted, *cis*- and *trans*-2,4-dioxa-9-aza- (type **I**), 2,4-dioxa-8-aza- (type **II**), and 2,4-dioxa-7-aza-3-phosphabicyclo[4.4.0]decane 3-oxides (type **III**) [3] (Scheme 1). These heterocycles are configuratively fixed and structurally constrained acetylcholine (7-aza and 9-aza isomers) or γ -homo-acetylcholine mimetics (8-aza isomers). Actually, we are completing the syntheses of all these organophosphates in the enantiomerically pure form (ee > 99%) and establishing their absolute configurations. Key compounds are the corresponding enantiomerically pure *cis*- and *trans*-diols **1–3** that are accessible from suitable starting materials such as appropriately substituted pyridinone or pyridine precursors.

Scheme 1



During our work on the preparation of the piperidinemethanols **1** and the 9-aza-3-phosphadecalins (type **I**, *Scheme 1*), we encountered several inconsistencies between chiroptical data and the assignment of the absolute configuration of the *cis*-configured 1-substituted ethyl 3-hydroxypiperidine-4-carboxylates [4–6] that conflicted with our results [7]. This fact prompted us to supply additional evidence for the absolute configuration, and we demonstrate that the current literature data [4–6] have to be revised.

2. Results and Discussion. – *Preparation and Characterization of the Ethyl (+)- and (–)-cis-1-Benzyl-3-hydroxypiperidine-4-carboxylates ((+)-5 and (–)-5).* 2.1. *Biological Reduction.* Following a known protocol [8], ethyl 1-benzyl-3-oxopiperidine-4-carboxylate (**4**) was reduced with bakers' yeast under nonfermenting conditions (*Scheme 2*). As expected, the dextrorotatory *cis*-3-hydroxy ester (+)-**5** was isolated as the main product (40%). Compared to the data in [8], our (+)-**5** had a significantly higher specific rotation ($[\alpha]_D = +41.2$ vs. $+27.35$) and an ee of 82% was found by HPLC (*Table*). However, in [8], the absolute configuration was not determined, but it had been tentatively assigned to be (3*R*,4*R*), in analogy to earlier findings and with respect to the ample theoretical and experimental background [8][9]. The stereochemistry and the stereoselectivity of NAD(H)-dependent oxido reductions are well investigated [9][10]. Bakers' yeast is known to belong to the group of E₃-type enzymes [11] that exhibit *pro*-(*R*)-*H/re*-face selectivity, and it shows pronounced *cis*-diastereoselectivity in the reduction of α -substituted cyclic ketones. Therefore, the main product (+)-**5** of the biological reduction of the piperidinone **4** is expected to have the configuration (3*R*,4*R*)¹.

Table. HPLC and Chiroptical Properties of the cis-Configured Reduction Products of Ethyl 1-Benzyl-3-oxopiperidine-4-carboxylate (4) under Various Conditions. HPLC Conditions: Chiralcel® OD-H (250 × 4.6 mm, hexane/PrOH, 12 : 1, flow rate 1 ml/min; R_s > 2).

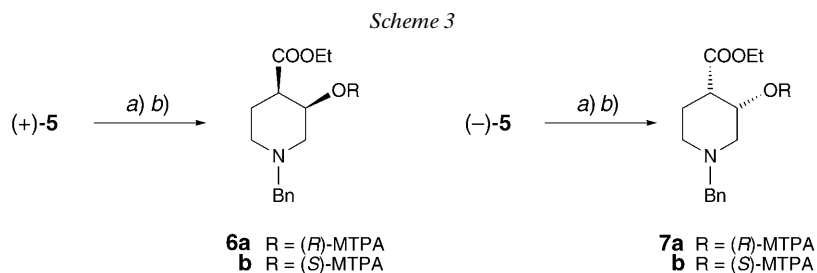
Reducing agent	<i>k'</i>	ee [%] ^{a)}	$[\alpha]_D$ ^{b)}	Product
NaBH ₄	2.17/2.75	–	–	(±)- 5
Bakers' yeast	2.19 ^{c)}	82	+41.2	(+)- 5 ^{c)}
[Ru{(+)-(<i>R</i>)-binap}Cl(cym)]Cl/H ₂	2.75	> 99 ^{d)}	–56.3 ^{d)}	(–)- 5
[Ru{(–)-(S)-binap}Cl(cym)]Cl/H ₂	2.19	> 99 ^{d)}	+55.6 ^{d)}	(+)- 5

^{a)} Determined according to area-%. ^{b)} *c* = 1, CHCl₃. ^{c)} Major enantiomer. ^{d)} After purification on Chiralcel® OD.

2.2. *Stereoselective Hydrogenations.* To prepare the enantiomeric *cis*-3-hydroxy ester (–)-**5** for unequivocal comparisons, the piperidinone **4** was catalytically hydrogenated with both [Ru{(+)-(*R*)-binap}Cl(cym)]Cl and [Ru{(–)-(S)-binap}Cl(cym)]Cl

¹⁾ The argumentation needs an auxiliary comment: Although the definition of *re* and *si* is strictly based on the priority rules [12], it has been shown that rather the bulkiness and the hydrophobic characteristics of the carbonyl substituents are determining the stereochemical outcome of biological reductions [9–11]. Hence, the synonyms R_L (large) and R_S (small) are more adequate. According to these considerations, C(4) is assigned as R_L, and C(2) as R_S in **4** and the 'biological' *re*-face is accurately specified as *si*, see also [8].

(*S*)-MTP-Cl (= (+)-(*S*)- α -methoxy- α -(trifluoromethyl)benzeneacetyl chloride) afforded the (*R*)-ester **6a**, and the corresponding (*S*)-ester **6b** was isolated after reaction of (+)-**5** with (–)-(*R*)-MTP-Cl. The same procedure was performed with (–)-**5** to yield the (*R*)-MTPA ester **7a** and the (*S*)-MTPA ester **7b**, respectively. From the $\delta(S) - \delta(R)$ values in the ^1H - and ^{19}F -NMR spectra of the **6a/6b** and the **7a/7b** couples, the (*3R*)-configuration for (+)-**5** and the (*3S*)-configuration for (–)-**5** could be unambiguously assigned (see *Exper. Part*)⁵. This result confirms the predicted stereochemical outcome of the [Ru(binap)]-catalyzed hydrogenations and fully corroborates the considerations on the biological reduction [8].

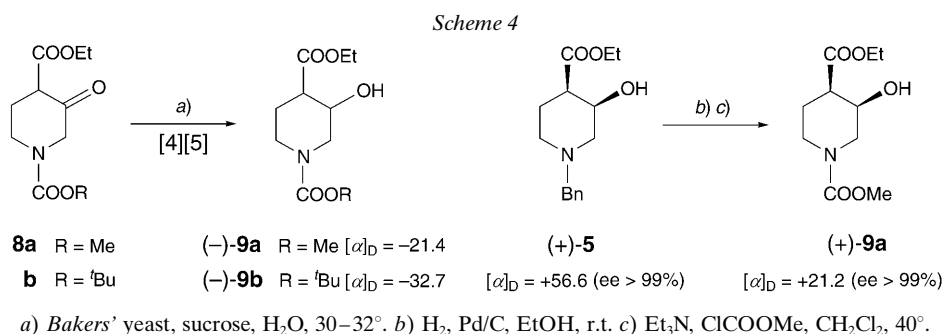


MTPA = 3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl

a) (–)-(*R*)- or (+)-(*S*)-MTP-Cl, resp., pyridine, r.t. b) Chromatography (SiO_2 , $\text{CH}_2\text{Cl}_2/\text{MeOH}$). (*R*)-MTP-Cl yields the (*S*)-MTPA ester and *vice versa*.

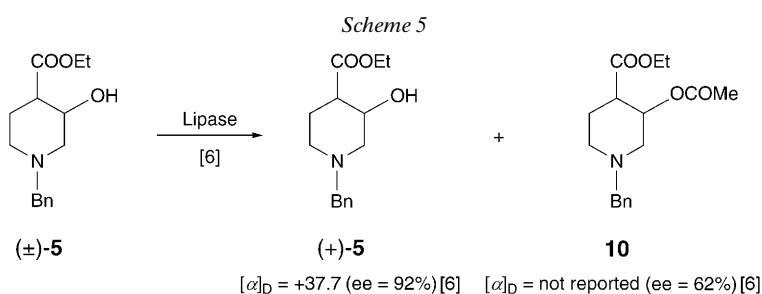
2.4. Transformation of (+)-**5** to the Carbamate (+)-**9a**. During our investigations, we encountered the laevorotatory 4-ethyl 1-methyl 3-hydroxypiperidine-1,4-dicarboxylate ((–)-**9a**; $[\alpha]_{\text{D}} = -21.4$) and laevorotatory 1-(*tert*-butyl) 4-ethyl 3-hydroxypiperidine-1,4-dicarboxylate ((–)-**9b**; $[\alpha]_{\text{D}} = -32.7$) that had been obtained after reduction of the 3-oxopiperidine-1,4-dicarboxylates **8a** and **8b** with fermenting bakers' yeast [4] [5] (Scheme 4). The compounds are very similar to our (+)-**5** and, according to [8], are assigned the expected (*3R*)-configuration, but the laevorotatory specific rotations were in conflict with our findings. However, as the electron-withdrawing *N*-substituents might significantly affect the conformation, a conclusion from the sign of the optical rotation to the absolute configuration was not applicable. To compare the chiroptical data reliably, the *N*-benzyl derivative (+)-**5** was transformed to the parent methyl carbamate (+)-**9a** (Scheme 4). The isolated compound was dextrorotatory ($[\alpha]_{\text{D}} = +21.2$), and due to its origin undoubtedly had the structure (+)-**9a** with (*3R,4R*)-configuration. Thus, (–)-**9a** has the (*3S,4S*)-configuration.

⁵) In principle, it was not assured *a priori* that the Mosher method is reliably applicable to such N-heterocyclic compounds. However, the fact that $\delta(S) - \delta(R) = 0$ Hz for H–C(3) in the MTPA ester couples **6a/6b** and **7a/7b** guarantees the quality of the experiments.



3. Conclusions. – Our results established that the structures of the 3-hydroxypiperidine-4-carboxylates mentioned above and derivatives thereof [4] [5]⁶⁾ have to be fitted with their chiroptical data.

Recently, the enzyme-catalyzed kinetic resolution of (\pm)-**5** was reported [6] to yield a dextrorotatory ethyl 1-benzyl-3-hydroxypiperidine-4-carboxylate ((**+**)-**5**; $[\alpha]_D = +37.7$, ee 92%) of absolute configuration (3*S*,4*S*), besides ethyl 3-(acetyloxy)-1-benzylpiperidine-4-carboxylate of absolute configuration (3*R*,4*R*) (Scheme 5). The absolute configuration has been assigned based on the chiroptical data and comparison with [4] [5]. According to our results, the dextrorotatory optical rotation clearly conflicts with the (3*S*)-configuration attributed to this 3-hydroxy ester (**+**)-**5** and its absolute value with the ee. Whereas the correct structures and stereodescriptors of the compounds are depicted in [4] [5], the result of [6] must be questioned more fundamentally as the stereochemical course of the kinetic resolution is not known.



4. Remarks. – The reasons for these inconsistencies are not obvious. Although [4] [5] explicitly refer to the basic experiments [8] where it is clearly stated that *bakers'* yeast reduction of piperidinone **4** predominantly yields the dextrorotatory, (3*R*)-configured *cis*-hydroxy ester (**+**)-**5**, the final conclusion was erroneous. Hence, it can be assumed that it might have a rather trivial origin, most probably such as unconventional drawings [4] followed by a C₂-rotation leading to the enantiomer [5], or reading and printing errors. Definitely, these inconsistencies have significant consequences on the interpre-

⁶⁾ The main derivatives are the corresponding methyl (3*R*,4*S*)-4-(hydroxymethyl)-3-oxypiperidine-1-carboxylates; unfortunately, there are no chiroptical data reported [5].

tation of subsequent investigations. Moreover, since piperidine-based compounds are pharmaceutically promising substances, the correctness of their structures is indispensable – last but not least from the viewpoint of patent, medicine, and the legal aspects connected therewith.

Considering further chemical aspects, the present report fully confirms the tentative assignments made earlier [8], delivers additional insight into the stereochemical outcome of [Ru^{II}(binap)]-catalyzed stereoselective hydrogenations of N-heterocyclic compounds, and demonstrates the applicability of the NMR *Mosher* method in the series of disubstituted piperidines.

A full account on the preparation of the enantiomerically pure four stereoisomeric 3-hydroxy esters **5** and **6**, the four stereoisomeric diols **1**, and the eight stereoisomeric 9-aza-3-phosphadecalins (type **I**, *Scheme 1*), in particular the determination of the absolute configurations and the inhibitory action on acetylcholinesterase will be presented in a subsequent report [14⁷].

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Experimental Part

1. *General*. See [3]. Enantioselective hydrogenations with {(+)-(1*R*)- and {(-)-(1*S*)-[1,1'-binaphthalene]-2,2'-diylbis[diphenylphosphine- κ P]}chloro[1,2,3,4,5,6- η]1-methyl-4-(1-methylethyl)benzene]ruthenium(1+) chloride ([Ru{(+)-(*R*)-binap}Cl(cym)]Cl- and [Ru{(-)-(*S*)-binap}Cl(cym)]Cl, resp.; *Fluka 14800* and *14801*, resp.) were performed in a high-pressure reactor (*Parr 452HC2*) equipped with a *Teflon*[®] vessel. The MTPA derivatives were prepared with (-)-(α *R*)- and (+)-(α *S*)- α -methoxy- α -(trifluoromethyl)benzeneacetyl chloride ((-)-(*R*)- and (+)-(*S*)-MTP-Cl, resp.; *Fluka 65363* and *65365*, resp., *ChiraSelect*. [α]_D²⁰: *Perkin-Elmer-241-MC* polarimeter with a *B.-Braun-Thermomix-1441* thermostat; 10-cm cell; in CHCl₃, *c* = 1. CC = Column chromatography. Anal. HPLC: *Pharmacia-LKB* HPLC pump 2248, *Hewlett-Packard-HP-1040 M* diode-array detection system, data handling on a *Hewlett-Packard-HP* Chemstation for LC, *Rev. A.04.02*; *Chiralcel*[®] *OD-H* (*Daicel Chemical Industries, Ltd.*) 5 μ , 250 \times 4.6 mm column; eluent hexane/ⁿPrOH 12 : 1, flow rate 1 ml/min, at r.t.; λ_{det} 220 nm. Prep. HPLC: *Applied-Biosystems-400* solvent-delivery system, *Applied-Biosystems-783A* programmable absorbance detector; *Chiralcel*[®] *OD* 10 μ , 250 \times 20 mm column; eluent hexane/EtOH 15 : 1, flow rate 5 ml/min, at r.t.; λ_{det} 254 nm. ee determinations by integration of the peak areas of the anal. HPLC separations (α = 1.26, *R*_s > 2).

2. *cis-3-Hydroxy Esters (+)-5 and (-)-5*. 2.1. (+)-Ethyl (3*R*,4*R*)-1-Benzyl-3-hydroxypiperidine-4-carboxylate ((+)-**5**). a) *Reduction with Bakers' Yeast*. Ethyl 1-benzyl-3-oxopiperidine-4-carboxylate hydrochloride (**4**·HCl; 2 g) was added to a suspension of commercial (*COOP*, Zurich) lyophilized bakers' yeast (130 g) and tap water (2 l) at 30°, and the mixture was gently shaken for 52 h. After centrifugation (8800 rpm, 15 min), the clear supernatant was continuously extracted with Et₂O, the extract concentrated and the residue dried (50°/0.05 Torr) to yield the crude products as a brownish oil (955 mg, 54%). CC (SiO₂, CH₂Cl₂/MeOH 98 : 2) afforded, from the earlier eluting fraction, (+)-**5** (648 mg, 37%; [α]_D = +41.2, ee 82%). The later eluting fraction yielded the (-)-*trans*-3-hydroxy ester (107 mg, 6%; [α]_D = -23.1, ee 95%)².

b) *Enantioselective Hydrogenation*. Ethyl 1-benzyl-3-oxopiperidine-4-carboxylate hydrochloride (**4**·HCl; 2.06 g) in EtOH (35 ml) was degassed (Ar, 30 min, r.t.), then [Ru{(-)-(*S*)-binap}Cl(cym)]Cl (50 mg) was added and pressurized with H₂ (120 bar) at 80° for 24 h. After cooling, the solvent was

7) The assignment of the absolute configuration of (+)-**5** has been fully confirmed by an X-ray crystallographic analysis of a *cis*-9-aza-3-phosphadecalin (type **I**) that is based on (+)-**5** [14].

evaporated, the oily brownish residue dissolved in sat. $\text{NaHCO}_3/\text{H}_2\text{O}$ and continuously extracted with Et_2O and the extract concentrated and dried (r.t./0.03 Torr): 1.72 g (94%) of the crude *cis*- and *trans*-3-hydroxy esters. CC (SiO_2 , $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 98:2) afforded from the earlier eluting fraction (+)-**5** (538 mg, 30%; ee 56%) and later the (+)-*trans*-3-hydroxy ester (359 mg, 20%; ee 81%)³⁾. The enantiomerically pure compounds were obtained after purification by prep. HPLC (*Chiralcel*[®] OD).

(+)-*trans*-3-Hydroxy ester: $[\alpha]_{\text{D}} = +25.2$, ee > 99%²⁾.

Data of (+)-**5**: Colorless, viscous oil. $[\alpha]_{\text{D}} = +55.6$. ¹H-NMR (600 MHz, CDCl_3): 7.32–7.25 (*m*, PhCH_2); 4.20 (*s*-like, $w_{1/2} \approx 8$, $\text{H}-\text{C}(3)$)⁸⁾; 4.18 (*q*, $^3J = 7.1$, MeCH_2); 3.54 (*s*, PhCH_2); 2.97 (*ddd*, $^2J = 11.6$, $^3J(2\text{eq},3) = 3.7$, $^4J(2\text{eq},6\text{eq}) = 1.8$, $\text{H}_{\text{eq}}-\text{C}(2)$); 2.88 (*br. dt*-like, $^2J = 11.5$, $^3J(6\text{eq},5\text{ax}) \approx ^3J(6\text{eq},5\text{eq}) \approx 3.5$, $^4J(6\text{eq},2\text{eq}) = 1.8$, $\text{H}_{\text{eq}}-\text{C}(6)$); 3.38 (*ddd*, $^3J(4,5\text{ax}) = 9.5$, $^3J(4,5\text{eq}) = 4.4$, $^3J(4,3) = 2.6$, $\text{H}-\text{C}(4)$); 2.22 (*dd*, $^2J = 11.6$, $^3J(2\text{ax},3) = 1.5$, $\text{H}_{\text{ax}}-\text{C}(2)$); 2.13–1.96 (*m, dt*- and *dq*-like, $^2J \approx ^3J \approx 11$, $^3J \approx 4$, $\text{H}_{\text{ax}}-\text{C}(5)$, $\text{H}_{\text{ax}}-\text{C}(6)$); 1.77 (*br. dq*-like, $^2J = 11$, $^3J(5\text{eq},4) \approx ^3J(5\text{eq},6\text{ax}) \approx ^3J(5\text{eq},6\text{eq}) \approx 3$, $\text{H}_{\text{eq}}-\text{C}(5)$); 1.27 (*t*, $^3J = 7.1$, MeCH_2). ¹³C-NMR (75.4 MHz, CDCl_3): 173.0 (COOEt); 137.5 (C(1')); 129.0 (C(3'), C(5')); 128.3 (C(2'), C(6')); 127.3 (C(4')); 66.3 (C(3)); 62.3 (PhCH_2); 60.5 (MeCH_2); 58.8 (C(2)); 51.9 (C(6)); 45.4 (C(4)); 22.2 (C(5)); 14.1 (MeCH_2). CI-MS (NH_3): 264 (100, $[M + \text{H}]^+$), 263 (18, M^+), 245 (25, $[M - \text{H}_2\text{O}]^+$).

2.2. (–)-*Ethyl* (3*S*,4*S*)-1-Benzyl-3-hydroxypiperidine-4-carboxylate ((–)-**5**). As described in *Exper. 2.1*, hydrogenation of **4**·HCl (2.68 g) in EtOH (35 ml) with $[\text{Ru}\{(+)-(R)\text{-binap}\}\text{Cl}(\text{cym})\text{Cl}]$ (50 mg) yielded 1.07 g (58%) of the crude mixture of diastereoisomers and, after chromatography, (–)-**5** (640 mg, 27%; ee 54%) and the (–)-*trans*-3-hydroxy ester (524 mg, 22%; ee 75%)³⁾. The enantiomerically pure compounds were obtained after purification with prep. HPLC (*Chiralcel*[®] OD).

(–)-*trans*-3-Hydroxy ester: $[\alpha]_{\text{D}} = -24.9$, ee > 99%²⁾.

Data of (–)-**5**: Colorless, viscous oil. $[\alpha]_{\text{D}} = -56.3$. ¹H- and ¹³C-NMR and MS: identical with those of (+)-**5**.

3. (R)- and (S)-MTPA Esters for the Determination of the Absolute Configuration. The 3-hydroxy ester (+)- or (–)-**5** (25 mg) was dissolved in dry pyridine (200 μl) and treated with (+)-(*S*)-MTP-Cl (25 μl , 1.5 equiv.) at r.t. for 24 h under Ar. Evaporation of the solvent and chromatographic purification (SiO_2 , $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 98:2) of the crude products afforded the (R)-MTPA esters **6a** and **7a**, resp. The same procedure was adopted for the reaction of (+)- or (–)-**5** with (–)-(*R*)-MTP-Cl to yield the (S)-MTPA esters **6b** and **7b**, resp. All MTPA derivatives were isolated in pure form as colorless, viscous oils: **6a** (27 mg, 60%), **6b** (34 mg, 75%), **7a** (32 mg, 71%), and **7b** (34 mg, 75%).

Data of the (R)- and (S)-MTPA Esters of (+)-**5**. *Ethyl* (3*R*,4*R*)-1-Benzyl-3-[(2*R*)-3,3,3-trifluoro-2-methoxy-1-oxo-2-phenylpropoxy]piperidine-4-carboxylate ((R)-MTPA ester; **6a**): ¹H-NMR (600 MHz, CDCl_3): 7.66 (*d*-like, $^3J = 7$), 7.53–7.22 (*m*) (PhCH_2 , Ph); 5.59 (*s*-like, $w_{1/2} \approx 12$, $\text{H}-\text{C}(3)$); 4.03, 3.96 (*AB* of ABX_3 , $^2J = 10.8$, $^3J(\text{AX}) = ^3J(\text{BX}) = 7.2$, MeCH_2); 3.59 (*s*, MeO); 3.59 (*AB*, $^2J = 13.5$, PhCH_2); 3.38 (*ddd*, $^2J = 13$, $^3J(2\text{eq},3) = 3$, $^4J(2\text{eq},6\text{eq}) = 1.5$, $\text{H}_{\text{eq}}-\text{C}(2)$); 3.01 (*br. d*, $^2J = 11$, $w_{1/2} \approx 18$, $\text{H}_{\text{eq}}-\text{C}(6)$); 2.51 (*dt*-like, $^3J(4,5\text{ax}) \approx 11$, $^3J(4,5\text{eq}) \approx ^3J(4,3) \approx 3$, $\text{H}-\text{C}(4)$); 2.22 (*br. d*, $^2J = 13$, $\text{H}_{\text{ax}}-\text{C}(2)$); 2.02–1.80 (*m*, $\text{CH}_2(5)$, $\text{H}_{\text{ax}}-\text{C}(6)$); 1.16 (*t*, X of ABX_3 , $^3J(\text{XA}) = ^3J(\text{XB}) = 7.1$, MeCH_2). ¹³C-NMR (75.4 MHz, CDCl_3): 172.1 (COOEt); 165.2 (COO(MTPA)); 137.3 (C(1')); 132.2 (C(1'')); 129.4 (C(3'), C(5')); 128.7 (C(3''), C(5'')); 128.2 (C(2'), C(6'), C(2''), C(6'')); 127.5 (C(4')); 127.1 (C(4'')); 71.8 (C(3)); 62.4 (PhCH_2); 60.7 (MeCH_2); 55.7 (MeO); 55.3 (C(2)); 51.8 (C(6)); 44.0 (C(4)); 22.8 (C(5)); 13.8 (MeCH_2). ¹⁹F-NMR (564.5 MHz, CDCl_3): –72.16. CI-MS (NH_3): 497 (100, $[M + \text{NH}_4]^+$), 479 (10, M^+), 263 (13, $[M - \text{MTPA}]^+$), 245 (25, $[M + \text{H} - \text{MTPA} - \text{H}_2\text{O}]^+$).

Ethyl (3*R*,4*R*)-1-Benzyl-3-[(2*S*)-3,3,3-trifluoro-2-methoxy-1-oxo-2-phenylpropoxy]piperidine-4-carboxylate ((S)-MTPA ester; **6b**): ¹H-NMR (600 MHz, CDCl_3): 7.53 (*d*-like, $^3J = 8$), 7.41–7.18 (*m*) (PhCH_2 , Ph); 5.59 (*s*-like, $w_{1/2} \approx 12$, $\text{H}-\text{C}(3)$); 4.05, 4.00 (*AB* of ABX_3 , $^2J = 10.8$, $^3J(\text{AX}) = ^3J(\text{BX}) = 7.1$, MeCH_2); 3.48 (*d*, $^4J(\text{Me},\text{F}) = 0.8$, MeO); 3.48, 3.46 (*AB*, $^2J = 13$, PhCH_2); 3.28 (*ddd*, $^2J = 13$, $^3J(2\text{eq},3) = 3$, $^4J(2\text{e},6\text{e}) = 1.5$, ($\text{H}_{\text{eq}}-\text{C}(2)$); 2.94 (*br. d*, $^2J = 10.5$, $w_{1/2} \approx 18$, $\text{H}_{\text{eq}}-\text{C}(6)$); 2.47 (*br. dt*-like, $^3J(4,5\text{ax}) \approx 9$, $w_{1/2} \approx 20$, $\text{H}-\text{C}(4)$); 2.18 (*br. d*, $^2J = 13$, $\text{H}_{\text{ax}}-\text{C}(2)$); 2.08–1.91 (*m*, $\text{CH}_2(5)$, $\text{H}_{\text{ax}}-\text{C}(6)$); 1.20 (*t*,

⁸⁾ According to the shape of the signal, $\text{H}-\text{C}(3)$ is equatorial, *i.e.*, $\text{OH}-\text{C}(3)$ is axial and the substituents at N(1) and C(4) are equatorial in the predominant conformation.

X of ABX_3 , $^3J(XA) = ^3J(XB) = 7.1$, $MeCH_2$). ^{13}C -NMR (75.4 MHz, $CDCl_3$): 172.4 (COOEt); 165.4 (COO (MTPA)); 137.3 (C(1')); 1321 (C(1'')); 129.4 (C(3'), C(5')); 128.6 (C(3''), C(5'')); 128.1 (C(2'), C(6'), C(2''), C(6'')); 127.6 (C(4')); 127.0 (C(4'')); 71.6 (C(3)); 62.4 (PhCH₂); 60.8 (MeCH₂); 55.6 (MeO); 55.2 (C(2)); 51.8 (C(6)); 44.1 (C(4)); 22.8 (C(5)); 13.9 (MeCH₂). ^{19}F -NMR (564.5 MHz, $CDCl_3$): -72.37.

$\Delta\delta(H) = \delta(S) - \delta(R)$ (in Hz⁹): H-C(3), 0⁵; H_{eq}-C(2), -60; H_{ax}-C(2), -24; MeCH₂, +12 and +24; MeCH₂, +24 → (3R)-configuration. $\Delta\delta(^{19}F) = \delta(S) - \delta(R)$ (in Hz): CF₃, -119 → (3R)-configuration.

Data of the (R)- and (S)-MTPA Esters of (-)-5 (**7a** and **7b**). Being enantiomeric compounds, **7a** and **6b** (**7a** = *ent*-**6b**) as well as **7b** and **6a** (**7b** = *ent*-**6a**) exhibited identical NMR-spectra. Only the diagnostically relevant signals are mentioned below⁹.

Ethyl (3S,4S)-1-Benzyl-3-[(2R)-3,3,3-trifluoro-2-methoxy-1-oxo-2-phenylpropoxy]piperidine-4-carboxylate ((R)-MTPA ester; **7a**): 1H -NMR (300 MHz, $CDCl_3$): 5.59 (*s*-like, $w_{1/2} \approx 12$, H-C(3)); 4.05, 4.00 (*AB* of ABX_3 , $^2J = 10.8$, $^3J(AX) = ^3J(BX) = 7.1$, MeCH₂); 3.28 (*ddd*, $^2J = 13$, $^3J(2eq,3) = 3$, $^4J(2e,6e) = 1.5$, H_{eq}-C(2)); 2.18 (*br. d.*, $^2J = 13$, H_{ax}-C(2)); 1.20 (*t.*, X of ABX_3 , $^3J(XA) = ^3J(XB) = 7.1$, MeCH₂). ^{19}F -NMR (564.5 MHz, $CDCl_3$): -72.33.

Ethyl (3S,4S)-1-Benzyl-3-[(2S)-3,3,3-trifluoro-2-methoxy-1-oxo-2-phenylpropoxy]piperidine-4-carboxylate ((S)-MTPA ester; **7b**): 1H -NMR (300 MHz, $CDCl_3$): 5.59 (*s*-like, $w_{1/2} \approx 12$, H-C(3)); 4.03, 3.96 (*AB* of ABX_3 , $^2J = 10.8$, $^3J(AX) = ^3J(BX) = 7.2$, MeCH₂); 3.38 (*ddd*, $^2J = 13$, $^3J(2eq,3) = 3$, $^4J(2eq,6eq) = 1.5$, H_{eq}-C(2)); 2.22 (*br. d.*, $^2J = 13$, H_{ax}-C(2)); 1.16 (*t.*, X of ABX_3 , $^3J(XA) = ^3J(XB) = 7.1$, MeCH₂). ^{19}F -NMR (564.5 MHz, $CDCl_3$): -72.11.

$\Delta\delta(H) = \delta(S) - \delta(R)$ (in Hz⁹): H-C(3), 0⁵; H_{eq}-C(2), +60; H_{ax}-C(2), +24; MeCH₂, -12 and -24; MeCH₂, -65 → (3S)-configuration. $\Delta\delta(^{19}F) = \delta(S) - \delta(R)$ (in Hz): CF₃, +124 → (3S)-configuration.

4. Transformation of (+)-5 to (+)-4-Ethyl 1-Methyl (3R,4R)-3-Hydroxypiperidine-1,4-dicarboxylate ((+)-**9a**). A soln. of (+)-5 (206 mg; ee > 99%) in abs. EtOH (25 ml) was hydrogenolyzed with 10% Pd/C (300 mg) by stirring under a slight pressure of H₂ (rubber balloon) at r.t. (4 h). The catalyst was removed by filtration over *Celite*, the filtrate concentrated and the resulting viscous oil (200 mg) dried. The crude product was dissolved in CH₂Cl₂ (20 ml), then Et₃N (120 μ l (87 mg), 1.1 equiv.) and methyl chloroformate (=methyl carbonochloridate; 66 μ l (81 mg) 1.1 equiv.) were added and kept under reflux (18 h). The mixture was dissolved in sat. NaHCO₃/H₂O and extracted with Et₂O, the extract concentrated, and the residue dried (50°/0.05 Torr): (+)-**9a** (180 mg, 99%; ee > 99%).

Data of (+)-**9a**: Colorless, viscous oil. $[\alpha]_D = +21.2$. 1H -NMR (300 MHz, $CDCl_3$): 4.19 (*q.*, $^3J = 7.1$, MeCH₂); 4.18 (*s*-like, $w_{1/2} \approx 14$, H-C(3))⁸; 3.70 (*s.*, MeO); 3.01 (*dd.*, $^2J = 14.5$, $^3J(2eq,3) = 2.7$, H_{eq}-C(2)); 2.88 (*td*-like, $^2J \approx ^3J(6ax,5ax) \approx 11$, $^3J(6ax,5eq) = 3.2$, H_{ax}-C(6))¹⁰; 2.56 (*ddd.*, $J = ^3J(4,5ax) = 11.8$, $^3J(4,5eq) = 4.2$, $^3J(4,3) = 2.5$, H-C(4)); 2.15–2.01 (*m.*, overlapped, *dd.*, *qd.*, and *br. dt*-like, H_{ax}-C(2), H_{ax}-C(5), H_{eq}-C(6)); 1.76 (*br. dq.*, $^2J = 13.5$, $^3J(5e,4) = 4.2$, $^3J(5eq,6eq) = 3.2$, H_{eq}-C(5)); 1.28 (*t.*, $^3J = 7.1$, MeCH₂). ^{13}C -NMR (75.4 MHz, $CDCl_3$): 172.8 (COOEt); 155.7 (COOMe); 64.1 (C(3)); 60.0 (MeCH₂); 51.8 (MeO); 48.0 (C(2)); 44.2 (C(4)); 42.1 (C(6)); 21.6 (C(5)); 13.1 (MeCH₂). CI-MS (NH₃): 232 (100, [M+H]⁺). EI-MS: 213 (17, [M-H₂O]⁺), 186 (11), 154 (5, [M-COOMe]⁺), 140 (100, [M-COOEt]⁺), 126 (6), 102 (17, COOEt⁺), 88 (10), 59 (8, COOMe⁺).

⁹) For the determination of the $\delta(S) - \delta(R)$ values of overlapped *m* in the couples **6a/6b** and **7a/7b**, the shape of the individual signals and their respective line frequencies were thoroughly compared; only the diagnostically relevant signals are indicated. For unambiguous additional comparisons, also MTPA esters starting from (\pm)-5, and from enantiomerically enriched (+)- and (-)-5 (ee ca. 60%) were analyzed. The data of the respective diastereoisomer pairs were consistent in every respect and showed the relative displacements as expected [17]. Since **6a** = *ent*-**7b** and **6b** = *ent*-**7a**, **6a** (3R,4R,2'R) and **7b** (3S,4S,2'S) as well as **6b** (3R,4R,2'S) and **7a** (3S,4S,2'R) have identical NMR spectra.

¹⁰) According to the multiplicity and the magnitude of the coupling constants, the signal has to be attributed to an axial proton (H_{ax}-C(6)). It should be noted that in all other compounds with the electron-donating *N*-benzyl substituent, the paramagnetically shifted H-C(6) is in an equatorial position.

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