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

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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

1 X = Y = CH_2, Z = BnN
2 X = CH_2, Y = BnN, Z = CH_2
3 X = BnN, Y = Z = CH_2

type **I** (9-aza)
type **II** (8-aza)
type **III** (7-aza)

Bn = $PhCH_2$

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*-configurated 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-hydroxypiperidene-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 E_3-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-*Configurated Reduction Products of Ethyl 1-Benzyl-3-oxopiperidine-4-carboxylate* (**4**) *under Various Conditions.* HPLC Conditions: *Chiralcel® OD-H* (250 × 4.6 mm, hexane/^{i}PrOH, 12 : 1, flow rate 1 ml/min; $R_s > 2$).

Reducing agent	k'	ee [%][a])	$[\alpha]_D$[b])	Product
$NaBH_4$	2.17/2.75	–	–	(±)-**5**
Bakers' yeast	2.19[c])	82	+41.2	(+)-**5**[c])
[Ru{(+)-(*R*)-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**

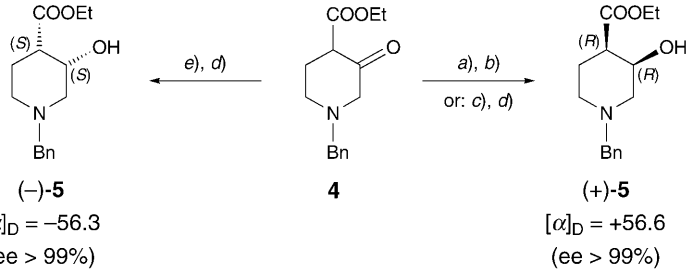
[a]) Determined according to area-%. [b]) $c = 1$, $CHCl_3$. [c]) Major enantiomer. [d]) After purification on *Chiralcel® OD*.

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].

(binap = [1,1′-binaphthalene]-2,2′-diylbis[diphenylphosphine], cym = *p*-cymene = (1-methyl-4-1-methylethyl)benzene; see *Exper. Part*) according to [13] (*Scheme 2*). In contrast to the biological reduction, the reactions proceeded with low diastereoselectivity (de < 10% in favor of the *cis*-isomer), thus providing access to all four stereoisomers of ethyl 1-benzyl-3-hydroxypiperidine-4-carboxylate[2]). Reaction with [Ru{(+)-(*R*)-binap}Cl(cym)]Cl yielded the laevorotatory *cis*-3-hydroxy ester (−)-**5** (ee 56%), whereas after analogous treatment with [Ru{(−)-(*S*)-binap}Cl(cym)]Cl the dextrorotatory *cis*-compound (+)-**5** (ee 54%) was isolated[3]). Chromatographic purification on *Chiralcel® OD* furnished the enantiomerically pure ethyl 1-benzyl-3-hydroxypiperidine-4-carboxylates (−)-**5** ($[\alpha]_D = -56.3$) and (+)-**5** ($[\alpha]_D = +56.6$) (*Table*).

Scheme 2



a) *Bakers'* yeast, H_2O, 30°. *b*) Chromatography (SiO_2, CH_2Cl_2/MeOH). *c*) [Ru{(−)-(*S*)-binap}Cl(cym)]Cl, H_2, EtOH, 150°, 100 bar. *d*) Prep. HPLC (*Chiracel® OD*, hexane/EtOH). *e*) [Ru{(+)-(*R*)-binap}Cl(cym)]Cl, H_2, EtOH, 150°, 100 bar.

2.3. *The Absolute Configurations.* At first, the absolute configurations of (+)- and (−)-**5** were tentatively inferred from the established stereochemical course of the asymmetric H-transfer to functionalized ketones [13] and the dynamic kinetic resolution in the [Ru^{II}(binap)]-catalyzed hydrogenations of 2-substituted 3-oxocarboxylic esters [15][4]): Hence, hydrogenation of **4** with [Ru{(+)-(*R*)-binap}Cl(cym)]Cl/H_2 would predominantly yield (3*S*)-**5**, whereas [Ru{(−)-(*S*)-binap}Cl(cym)]Cl/H_2 would afford mainly (3*R*)-**5**.

Finally, the absolute configurations were determined by the high-field ^{1}H-NMR application of the *Mosher* method [17] (*Scheme 3*). Esterification of (+)-**5** with (+)-

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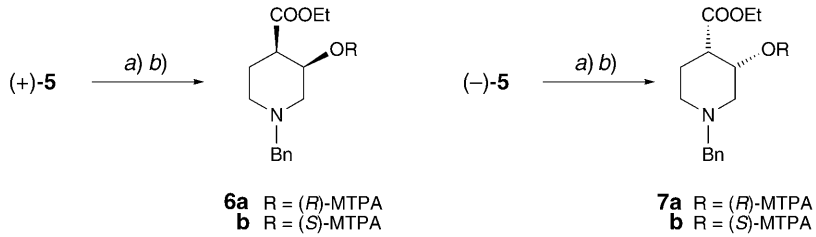
[2]) In this report, the discussion is restricted to the *cis*-hydroxy esters. A full account on the preparation and the characterization of the four stereoisomeric, enantiomerically pure ethyl 1-benzyl-3-hydroxypiperidine-4-carboxylates will be presented later [14].

[3]) Although the hydrogenation conditions were optimized, the low ee values are unsatisfactory. This fact is due to the coordinative interactions of the nonbonding electron pair of the *N*-benzyl group with the catalyst. Electron-withdrawing protecting groups such as Ts, 4-bromobenzoyl, *etc.*, give an increased selectivity up to ee *ca.* 90% [14].

[4]) According to the experimental results [13][15], it can be concluded that (+)-(*R*)-binap has predominantly *si*-face and (−)-(*S*)-binap *re*-face selectivity, irrespective of the bulkiness of the substituents that only affects the ee values. We have verified this empirical finding in several applications [14][16]. Moreover, cyclic ketones are hydrogenated with pronounced *anti*-selectivity in CH_2Cl_2 [13], whereas the de is *ca.* 0 in EtOH [15].

(*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 ^{1}H- and ^{19}F-NMR spectra of the **6a**/**6b** and the **7a**/**7b** couples, the (3*R*)-configuration for (+)-**5** and the (3*S*)-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].

Scheme 3



a) (−)-(*R*)- or (+)-(*S*)-MTP-Cl, resp., pyridine, r.t. *b*) Chromatograpy (SiO_2, CH_2Cl_2/MeOH). (*R*)-MTP-Cl yields the (*S*)-MTPA ester and *vica 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**; $[\alpha]_D=-21.4$) and laevorotatory 1-(*tert*-butyl) 4-ethyl 3-hydroxypiperidine-1,4-dicarboxylate ((−)-**9b**; $[\alpha]_D=-32.7$) 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 (3*R*)-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 ($[\alpha]_D=+21.2$), and due to its origin undoubtedly had the structure (+)-**9a** with (3*R*,4*R*)-configuration. Thus, (−)-**9a** has the (3*S*,4*S*)-configuration.

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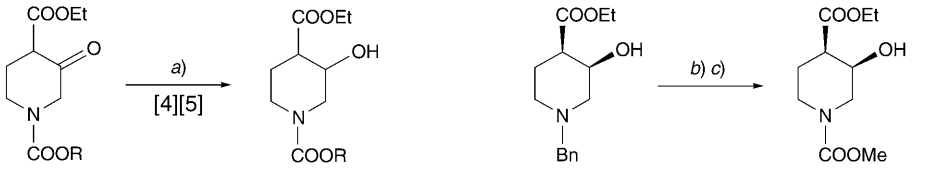
[5]) In principle, it was not assured *a priori* that the *Mosher* method is reliably applicable to such N-heterocyclic compounds. However, the fact that $\delta(S)-\delta(R)=0$ Hz for H−C(3) in the MTPA ester couples **6a**/**6b** and **7a**/**7b** guarantees the quality of the experiments.

Scheme 4



8a R = Me (–)-**9a** R = Me $[\alpha]_D$ = –21.4 (+)-**5** (+)-**9a**

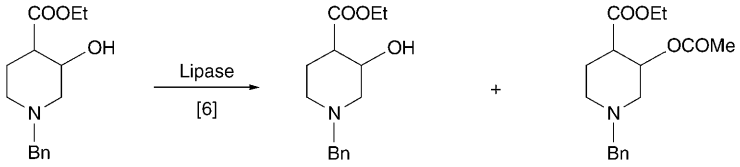
b R = ^{t}Bu (–)-**9b** R = ^{t}Bu $[\alpha]_D$ = –32.7 $[\alpha]_D$ = +56.6 (ee > 99%) $[\alpha]_D$ = +21.2 (ee > 99%)

a) *Bakers'* yeast, sucrose, H_2O, 30–32°. *b*) H_2, Pd/C, EtOH, r.t. *c*) Et_3N, ClCOOMe, CH_2Cl_2, 40°.

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 (±)-**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.

Scheme 5



(±)-**5** (+)-**5** **10**

$[\alpha]_D$ = +37.7 (ee = 92%) [6] $[\alpha]_D$ = not reported (ee = 62%) [6]

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*)-configurated *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 C_2-rotation leading to the enatiomer [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 [14][7]).

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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-κP]}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 (−)-(αR)- and (+)-(αS)-α-methoxy-α-(trifluoromethyl)benzeneacetyl chloride ((−)-(*R*)- and (+)-(*S*)-MTP-Cl, resp.; *Fluka 65363* and *65365*, resp., *ChiraSelect.* $[\alpha]_D^{20}$: *Perkin-Elmer-241-MC* polarimeter with a *B.-Braun-Thermomix-1441* thermostat; 10-cm cell; in $CHCl_3$, $c = 1$. 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 × 4.6 mm column; eluent hexane/^{i}PrOH 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 × 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 ($\alpha = 1.26$, $R_s > 2$).

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 Et_2O, the extract concentrated and the residue dried (50°/0.05 Torr) to yield the crude products as a brownish oil (955 mg, 54%). CC (SiO_2, CH_2Cl_2/MeOH 98 : 2) afforded, from the earlier eluting fraction, (+)-**5** (648 mg, 37%; $[\alpha]_D = +41.2$, ee 82%). The later eluting fraction yielded the (−)-*trans*-3-hydroxy ester (107 mg, 6%; $[\alpha]_D = -23.1$, 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 H_2 (120 bar) at 80° for 24 h. After cooling, the solvent was

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[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. $NaHCO_3/H_2O$ 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, CH_2Cl_2/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%[2])[3]). The enantiomerically pure compounds were obtained after purification by prep. HPLC (*Chiralcel® OD*).

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

Data of (+)-**5**: Colorless, viscous oil. $[\alpha]_D = +55.6$. ^{1}H-NMR (600 MHz, $CDCl_3$): 7.32–7.25 (*m*, *Ph*CH_2); 4.20 (*s*-like, $w_{1/2} \approx 8$, H–C(3))[8]); 4.18 (*q*, $^3J = 7.1$, MeCH_2); 3.54 (*s*, PhCH_2); 2.97 (*ddd*, $^2J = 11.6$, $^3J(2eq,3) = 3.7$, $^4J(2eq,6eq) = 1.8$, H_{eq}–C(2)); 2.88 (br. *dt*-like, $^2J = 11.5$, $^3J(6eq,5ax) \approx {}^3J(6eq,5eq) \approx 3.5$, $^4J(6eq,2eq) = 1.8$, H_{eq}–C(6)); 3.38 (*ddd*, $^3J(4,5ax) = 9.5$, $^3J(4,5eq) = 4.4$, $^3J(4,3) = 2.6$, H–C(4)); 2.22 (*dd*, $^2J = 11.6$, $^3J(2ax,3) = 1.5$, H_{ax}–C(2)); 2.13–1.96 (*m*, *dt*- and *dq*-like, $^2J \approx {}^3J \approx 11$, $^3J \approx 4$, H_{ax}–C(5), H_{ax}–C(6)); 1.77 (br. *dq*-like, $^2J = 11$, $^3J(5eq,4) \approx {}^3J(5eq,6ax) \approx {}^3J(5eq,6eq) \approx 3$, H_{eq}–C(5)); 1.27 (*t*, $^3J = 7.1$, *Me*CH_2). ^{13}C-NMR (75.4 MHz, $CDCl_3$): 173.0 (*C*OOEt); 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 (Ph*C*H_2); 60.5 (Me*C*H_2); 58.8 (C(2)); 51.9 (C(6)); 45.4 (C(4)); 22.2 (C(5)); 14.1 (*Me*CH_2). CI-MS (NH_3): 264 (100, $[M+H]^+$), 263 (18, M^+), 245 (25, $[M-H_2O]^+$).

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 [Ru{(+)-(*R*)-binap}Cl(cym)]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%[2])[3]). The enantiomerically pure compounds were obtained after purification with prep. HPLC (*Chiralcel® OD*).

(−)-trans-*3-Hydroxy ester:* $[\alpha]_D = -24.9$, ee > 99%[2]).

Data of (−)-**5**: Colorless, viscous oil. $[\alpha]_D = -56.3$. ^{1}H- and ^{13}C-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, CH_2Cl_2/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**): ^{1}H-NMR (600 MHz, $CDCl_3$): 7.66 (*d*-like, $^3J = 7$), 7.53–7.22 (*m*) (*Ph*CH_2, Ph); 5.59 (*s*-like, $w_{1/2} \approx 12$, H–C(3)); 4.03, 3.96 (*AB* of ABX_3, $^2J = 10.8$, $^3J(AX) = {}^3J(BX) = 7.2$, MeC$H_2$); 3.59 (*s*, MeO); 3.59, 3.48 (*AB*, $^2J = 13.5$, PhCH_2); 3.38 (*ddd*, $^2J = 13$, $^3J(2eq,3) = 3$, $^4J(2eq,6eq) = 1.5$, H_{eq}–C(2)); 3.01 (br. *d*, $^2J = 11$, $w_{1/2} \approx 18$, H_{eq}–C(6)); 2.51 (*dt*-like, $^3J(4,5ax) \approx 11$, $^3J(4,5eq) \approx {}^3J(4,3) \approx 3$, H–C(4)); 2.22 (br. *d*, $^2J = 13$, H_{ax}–C(2)); 2.02–1.80 (*m*, CH_2(5), H_{ax}–C(6)); 1.16 (*t*, *X* of ABX_3, $^3J(XA) = {}^3J(XB) = 7.1$, *Me*$CH_2$). ^{13}C-NMR (75.4 MHz, $CDCl_3$): 172.1 (*C*OOEt); 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 (Ph*C*H_2); 60.7 (Me*C*H_2); 55.7 (MeO); 55.3 (C(2)); 51.8 (C(6)); 44.0 (C(4)); 22.8 (C(5)); 13.8 (*Me*CH_2)). ^{19}F-NMR (564.5 MHz, $CDCl_3$): −72.16. CI-MS (NH_3): 497 (100, $[M+NH_4]^+$), 479 (10, M^+), 263 (13, $[M-\text{MTPA}]^+$), 245 (25, $[M+H-\text{MTPA}-H_2O]^+$).

*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**): ^{1}H-NMR (600 MHz, $CDCl_3$): 7.53 (*d*-like, $^3J = 8$), 7.41–7.18 (*m*) (*Ph*CH_2, Ph); 5.59 (*s*-like, $w_{1/2} \approx 12$, H–C(3)); 4.05, 4.00 (*AB* of ABX_3, $^2J = 10.8$, $^3J(AX) = {}^3J(BX) = 7.1$, MeC$H_2$); 3.48 (*d*, ^4J(Me,F) = 0.8, MeO); 3.48, 3.46 (*AB*, $^2J = 13$, PhCH_2); 3.28 (*ddd*, $^2J = 13$, $^3J(2eq,3) = 3$, $^4J(2e,6e) = 1.5$, (H_{eq}–C(2)); 2.94 (br. *d*, $^2J = 10.5$, $w_{1/2} \approx 18$, H_{eq}–C(6)); 2,47 (br. *dt*-like, $^3J(4,5ax) \approx 9$, $w_{1/2} \approx 20$, H–C(4)); 2.18 (br. *d*, $^2J = 13$, H_{ax}–C(2)); 2.08–1.91 (*m*, CH_2(5), H_{ax}–C(6)); 1.20 (*t*,

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[8]) According to the shape of the signal, H–C(3) is equatorial, *i.e.*, OH–C(3) is axial and the substituents at N(1) and C(4) are equatorial in the predominant conformation.

X of ABX_3, $^3J(XA)=^3J(XB)=7.1$, *Me*CH_2). ^{13}C-NMR (75.4 MHz, $CDCl_3$): 172.4 (*C*OOEt); 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 (Ph*C*H_2); 60.8 (Me*C*H_2); 55.6 (MeO); 55.2 (C(2)); 51.8 (C(6)); 44.1 (C(4)); 22.8 (C(5)); 13.9 (*Me*CH_2). ^{19}F-NMR (564.5 MHz, $CDCl_3$): −72.37.

$\Delta\delta(^1H)=\delta(S)-\delta(R)$ (in Hz)[9]): H−C(3), 0[5]); H_{eq}−C(2), −60; H_{ax}−C(2), −24; MeCH_2, +12 and +24; *Me*CH_2, +24 → (3*R*)-configuration. $\Delta\delta(^{19}F)=\delta(S)-\delta(R)$ (in Hz): CF_3, −119 → (3*R*)-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 below[9]).

*Ethyl (3*S*,4*S*)-1-Benzyl-3-[(2*R*)-3,3,3-trifluoro-2-methoxy-1-oxo-2-phenylpropoxy]piperidine-4-carboxylate* ((*R*)-MTPA ester; **7a**): ^{1}H-NMR (300 MHz, $CDCl_3$): 5.59 (*s*-like, $w_{1/2}\approx12$, H−C(3)); 4.05, 4.00 (*AB* of ABX_3, $^2J=10.8$, $^3J(AX)=^3J(BX)=7.1$, MeCH_2); 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, $^3J(XA)=^3J(XB)=7.1$, *Me*CH_2). ^{19}F-NMR (564.5 MHz, $CDCl_3$): −72.33.

*Ethyl (3*S*,4*S*)-1-Benzyl-3-[(2*S*)-3,3,3-trifluoro-2-methoxy-1-oxo-2-phenylpropoxy]piperidine-4-carboxylate* ((*S*)-MTPA ester; **7b**): ^{1}H-NMR (300 MHz, $CDCl_3$): 5.59 (*s*-like, $w_{1/2}\approx12$, H−C(3)); 4.03, 3.96 (*AB* of ABX_3, $^2J=10.8$, $^3J(AX)=^3J(BX)=7.2$, MeCH_2); 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, $^3J(XA)=^3J(XB)=7.1$, *Me*CH_2). ^{19}F-NMR (564.5 MHz, $CDCl_3$): −72.11.

$\Delta\delta(^1H)=\delta(S)-\delta(R)$ (in Hz)[9]): H−C(3), 0[5]); H_{eq}−C(2), +60; H_{ax}−C(2), +24; MeCH_2, −12 and −24; *Me*CH_2, −65 → (3*S*)-configuration. $\Delta\delta(^{19}F)=\delta(S)-\delta(R)$ (in Hz): CF_3, +124 → (3*S*)-configuration.

4. *Transformation of* (+)-**5** *to (+)-*4*-Ethyl 1-Methyl (3*R*,4*R*)-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 H_2 (rubber balloon) at r.t. (4 h). The catalyst was removed by filtration over *Celite*, the filtrate concentrated and the resultig viscous oil (200 mg) dried. The crude product was dissolved in CH_2Cl_2 (20 ml), then Et_3N (120 µl (87 mg), 1.1 equiv.) and methyl chloroformate (= methyl carbonochloridate; 66 µl (81 mg) 1.1 equiv.) were added and kept under reflux (18 h). The mixture was dissolved in sat. $NaHCO_3/H_2O$ and extracted with Et_2O, the extract concentrated, and the residue dried (50°/0.05 Torr): (+)-**9a** (180 mg, 99%; ee > 99%).

Data of (+)-**9a**: Colorless, viscous oil. $[\alpha]_D=+21.2$. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.19 (*q*, $^3J=7.1$, MeCH_2)); 4.18 (*s*-like, $w_{1/2}\approx14$, 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)≈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*, $^3J=7.1$, *Me*CH_2). ^{13}C-NMR (75.4 MHz, $CDCl_3$): 172.8 (*C*OOEt); 155.7 (*C*OOMe); 64.1 (C(3)); 60.0 (Me*C*H_2); 51.8 (MeO); 48.0 (C(2)); 44.2 (C(4)); 42.1 (C(6)); 21.6 (C(5)); 13.1 (*Me*CH_2)). CI-MS (NH_3): 232 (100, $[M+H]^+$). EI-MS: 213 (17, $[M-H_2O]^+$), 186 (11), 154 (5, $[M-COOMe]^+$), 140 (100, $[M-COOEt]^+$), 126 (6), 102 (17, $COOEt^+$), 88 (10), 59 (8, $COOMe^+$).

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[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 (±)-**5**, and from enatiomerically 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** (3*R*,4*R*,2′*R*) and **7b** (3*S*,4*S*,2′*S*) as well as **6b** (3*R*,4*R*,2′*S*) and **7a** (3*S*,4*S*,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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