

# The Absolute Configuration of the (+)- and (–)-*cis*- and (+)- and (–)-*trans*-1-Benzyl-4-hydroxypiperidine-3-methanols: An Unusual Application of the <sup>1</sup>H-NMR-Mosher Method

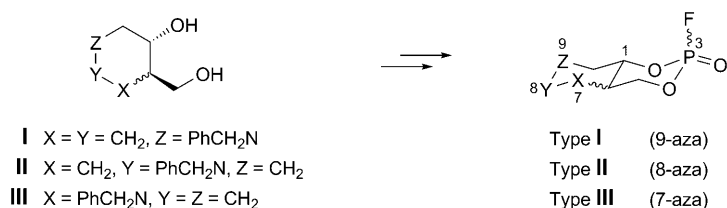
by Christian Clerc, Igor Matarazzo, and Peter Ruedi\*

Organisch-chemisches Institut der Universität Zürich, Winterthurerstrasse 190, CH-8057 Zürich  
(phone: +41-44-6354241; e-mail: peru@oci.uzh.ch)

The enantiomerically pure title compounds were prepared and the absolute configurations assigned by the high-field <sup>1</sup>H-NMR application of the Mosher method on the bis-MTPA derivatives (MTPA =  $\alpha$ -methoxy- $\alpha$ -(trifluoromethyl)benzeneacetic acid). The final evidence for the adaptability of the procedure was effected by X-ray crystallographic analyses. The absolute configurations of the *cis*- and *trans*-1-benzyl-4-hydroxypiperidine-3-methanols are as follows: (+)-(3*S*,4*S*) and (–)-(3*R*,4*R*) (*cis*), and (+)-(3*R*,4*S*) and (–)-(3*S*,4*R*) (*trans*), respectively (Scheme 2). Nonfermenting bakers' yeast reduction of methyl 1-benzyl-4-oxopiperidine-3-carboxylate afforded (+)-methyl (3*R*,4*S*)-1-benzyl-4-hydroxypiperidine-3-carboxylate (de > 97%, ee > 99%) which was further reduced to the (+)-(3*S*,4*S*)-diol (Scheme 3). The result confirms the stereochemical outcome of the biological reduction with *re*-face selectivity and *cis*-diastereoselectivity as predicted for bakers' yeast. The 4-hydroxypiperidine-3-methanols are the key starting compounds for the synthesis of the enantiomerically pure P(3)-axially and P(3)-equatorially substituted *cis*- and *trans*-configured 8-benzyl-2,4-dioxa-8-aza-3-phosphadecalin 3-oxides (= 8-benzyl-2,4-dioxa-8-aza-3-phospha-bicyclo[4.4.0]decane 3-oxides) representing  $\gamma$ -homo-acetylcholine mimetics.

**1. Introduction.** – In the course of our studies on the 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) as racemates [3] (Scheme 1). These heterocycles are configuratively fixed and conformationally constrained acetylcholine (7-aza- and 9-aza isomers) or  $\gamma$ -homo-acetylcholine mimetics (8-

Scheme 1



aza isomers). Actually, we have completed the syntheses of all these organophosphates in the enantiomerically pure form (ee > 99%) and established their absolute configurations. Key compounds are the respective *cis*- and *trans*-diols **I–III** that are accessible from suitable starting materials such as appropriately substituted piperidinone or pyridine precursors.

During our work on the preparation of the enantiomerically pure piperidinemethanols **II** and the 8-aza-3-phosphadecalins (*Type II, Scheme 1*) [4], we became aware that the absolute configurations of the title compounds are not adequately described in the current literature. In the present report, we conclusively assign the absolute configurations of the *cis*- and *trans*-configured 4-hydroxypiperidine-3-methanols and the respective correlation with the chiroptical data.

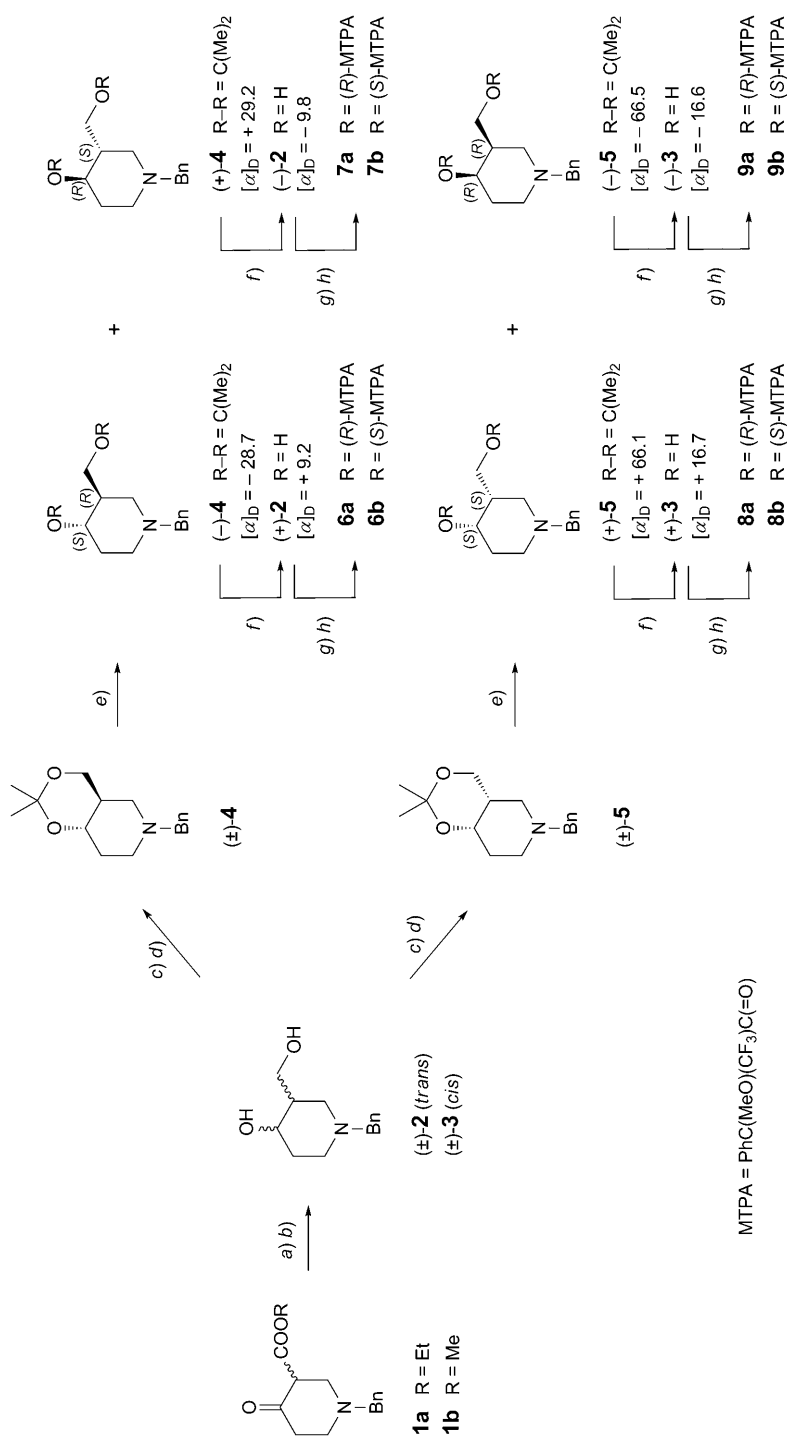
**2. Results and Discussion.** – 2.1. *Preparation of the (+)- and (–)-cis- and (+)- and (–)-trans-4-Hydroxypiperidine-3-methanols* ((+)- and (–)-**3**, and (+)- and (–)-**2**, resp.). Following the protocol for the preparation of the racemic compounds [3], ethyl 1-benzyl-4-oxopiperidine-3-carboxylate (**1a**) was reduced with NaBH<sub>4</sub>, the resulting mixture (±)-**2**/(±)-**3** (ca. 1:2) transformed *in situ* into the acetonides (±)-**4**/(±)-**5** and the diastereoisomers separated by chromatography (SiO<sub>2</sub>). Prep. HPLC (*Chiralcel*<sup>®</sup> OD) of the pure *trans*- and *cis*-isomers (±)-**4** and (±)-**5**, respectively, afforded the optically active acetonides (+)-**4** (*k'* = 2.60, ee > 99%), (–)-**4** (*k'* = 2.22, ee > 98%)<sup>1)</sup>, (+)-**5** (*k'* = 2.00, ee > 99%), and (–)-**5** (*k'* = 3.11, ee > 99%), resp. (*Scheme 2*) [4]. Hydrolysis of the respective acetonides gave the 1-benzyl-4-hydroxypiperidine-3-methanols (+)-**2** ([α]<sub>D</sub> = +9.2, ee > 98%)<sup>1)</sup>, (–)-**2** ([α]<sub>D</sub> = –9.8, ee > 99%), (+)-**3** ([α]<sub>D</sub> = +16.7, ee > 99%), and (–)-**3** ([α]<sub>D</sub> = –16.6, ee > 99%), respectively (*Scheme 2*).

2.2. *The Absolute Configurations of the Diols (+)- and (–)-2 and (+)- and (–)-3*. The absolute configurations of the diols (+)- and (–)-**2** and (+)- and (–)-**3** were tentatively inferred from an unusual extension of the high-field NMR application of the Mosher method [5]. As discussed earlier [6], it was not assured *a priori* that this procedure is reliably applicable to our N-heterocyclic compounds. Although the extension to the bis-(*R*)-MTPA derivatives **6a–9a** and the bis-(*S*)-MTPA derivatives **6b–9b** (*Scheme 2*) renders the concept even more doubtful, the respective MTPA esters were prepared and their <sup>1</sup>H-NMR spectra analyzed (MPTA = α-methoxy-α-(trifluoromethyl)benzeneacetic acid). Esterification of (+)- and (–)-**2** with (+)-(*S*)-MTPA–Cl (= (+)-(*S*)-α-methoxy-α-(trifluoromethyl)benzeneacetyl chloride) afforded the (*R*)-esters **6a** and **7a**, and the corresponding (*S*)-esters **6b** and **7b** were isolated after reaction of (+)- and (–)-**2** with (–)-(*R*)-MTPA–Cl. The same procedure was performed with (+)- and (–)-**3** to yield the (*R*)-MTPA esters **8a** and **9a** and the (*S*)-MTPA esters **8b** and **9b** (*Scheme 2*).

In the *trans*-series, the thorough analysis of the <sup>1</sup>H-NMR data led to a provisional assignment of the absolute configurations such as (+)-(3*R*,4*S*)-**2**, and (–)-(3*S*,4*R*)-**2**.

<sup>1)</sup> Although the method had been optimized to afford enantiomerically pure (–)-**4** ([α]<sub>D</sub> = –29.3, ee > 99%) in rather small amounts and the resolution is more than satisfactory (*R*<sub>S</sub> > 4), bigger fractions of (–)-**4** did not exceed ee > 98%. As a consequence, (+)-**2** did not exceed ee > 98%.

Scheme 2



a)  $\text{NaBH}_4$ ,  $\text{Na}_2\text{CO}_3$ ,  $i\text{-PrOH}$ ,  $10^\circ$  (*cis/trans* ca. 1:2). b)  $\text{LiAlH}_4$ ,  $\text{Et}_2\text{O}$ , r.t. (*cis/trans* ca. 1:1). c)  $\text{Me}_2\text{C}(\text{OMe})_2$ ,  $\text{TsOH}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $d$   $\text{CC}(\text{SiO}_2, \text{hexane}/\text{Et}_2\text{O})$ . For Steps a) – d), see [3]. e) Prep. HPLC (*Chiralcel*<sup>®</sup> OD, hexane/ $\text{EtOH}$ ). f) In  $\text{HCl}$ ,  $60^\circ$ . g)  $(-)\text{-}(R)\text{-}$  or  $(+)\text{-}(S)\text{-MTPA-Cl}$ , resp.,  $\text{Et}_3\text{N}$ ,  $N,N$ -dimethylpyridin-4-amine (DMAP),  $\text{CH}_2\text{Cl}_2$ , r.t. (note:  $(R)\text{-MTPA-Cl}$  yields the  $(S)\text{-MTPA}$  ester, and vice versa). h)  $\text{CC}(\text{SiO}_2, \text{AcOEt})$ .  $[\alpha]_D$  in acetone ( $c=1$ ), ee > 99% ((+)-**2**, (–)-**4**: ee > 98%).

The results were self-contained, in particular, the  $\Delta\delta$  values ( $=\delta(S)-\delta(R)$ ) of the diagnostically relevant signals were consistent: For the couple **6a/6b**, we observed  $\Delta\delta(\text{CH}_2(2) \text{ and } \text{H}-\text{C}(3)) > 0$  and  $\Delta\delta(\text{CH}_2(5)) < 0$ , and the inverse was found in the couple **7a/7b** (see *Exper. Part*)<sup>2</sup>. But the fact that  $\Delta\delta(\text{H}-\text{C}(4)) = \pm 0.01$  for **6a/6b** and **7a/7b** is indicative for a deviation from the ideal conformation of the MTPA moiety<sup>3</sup>, and, as a consequence, the reliability of the experiment is significantly reduced. Hence, the assignments of the absolute configurations are arguable and must be verified by an independent method. The X-ray crystallographic analysis of **6b** furnished the definite evidence (*Fig.*)<sup>4</sup>. It fully corroborated the assigned absolute configuration of the *trans*-4-hydroxypiperidine-3-methanols: (+)-(3*R*,4*S*)-**2** (*cf. Fig.*) and (–)-(3*S*,4*R*)-**2**. Moreover, the crystal structure demonstrated that the conformation of the diagnostically relevant moiety at C(4) coincides with the assumed one<sup>3</sup>. In contrast, the MPTA–OCH<sub>2</sub> group at C(3) adopts the *anti*-conformation of C=O and CF<sub>3</sub> that results in the inversed relative position of the shielding phenyl group, thus suggesting that the observed  $\Delta\delta(\text{H}-\text{C}(4)) \neq 0$  is due to this additional MTPA moiety.

The situation was more delicate in the conformationally flexible *cis*-series (**8a/8b** and **9a/9b**), and the experimental data were ambiguous. In particular, the reliability of an interpretation was significantly reduced due to  $\Delta\delta(\text{H}-\text{C}(4)) = \pm 0.07^3$  for **8a/8b** and **9a/9b**, and further considerations had to be made. However, in the absence of an X-ray crystallographic analysis of a *cis*-configured MTPA derivative, the rationale is based on the comparison of relative differences and remains speculative: According to the <sup>1</sup>H-NMR spectra, the MPTA–O group at C(4) is axial<sup>5</sup>), and, under the assumption that its conformation approximates the idealized one as found for **6b**<sup>3</sup>), the MTPA phenyl group is situated partly under the piperidine ring. As a consequence, shielding is expected mainly for H<sub>ax</sub>–C(2), H<sub>eq</sub>–C(5), and CH<sub>2</sub>(6) ( $\Delta\delta < 0$  for **8a/8b**), whereas H<sub>eq</sub>–C(2), H–C(3), and H<sub>ax</sub>–C(5) should only be marginally affected ( $\Delta\delta > 0$  for **8a/8b**), and *vice versa* for **9a/9b**. Moreover, due to the assumed steric environment for **8b** (2'*S*,3*S*,4*S*) and **9a** (2'*R*,3*R*,4*R*)<sup>2</sup>), the diamagnetic effect is expected to be stronger on H<sub>ax</sub>–C(5) and H<sub>ax</sub>–C(6) than on H<sub>ax</sub>–C(2) and H<sub>eq</sub>–C(5). The argumentation is inverse for **8a** (2'*R*,3*S*,4*S*) and **9b** (2'*S*,3*R*,4*R*)<sup>2</sup>).

<sup>2</sup>) Since **6a** = *ent*-**7b** and **6b** = *ent*-**7a**, **6a** (2'*R*,3*R*,4*S*) and **7b** (2'*S*,3*S*,4*R*), as well as **6b** (2'*S*,3*R*,4*S*) and **7a** (2'*R*,3*S*,4*R*) have identical NMR spectra. The same holds for **8a** (2'*R*,3*S*,4*S*) = *ent*-**9b** and **8b** (2'*S*,3*S*,4*S*) = *ent*-**9a**.

<sup>3</sup>) The theoretical prerequisite for the success and reliability of the <sup>1</sup>H-NMR Mosher experiments is that the MTPA moiety adopts an idealized conformation where the H-atom at the initially OH-substituted stereogenic center, the C=O, and the CF<sub>3</sub> groups lie in the same plane in a relative *syn*-arrangement [5]. Therefore, an essential quality factor for an experiment is the equal chemical shift ( $\Delta\delta = 0$ ) for the H-atom at the MPTA–O-substituted stereogenic center in both the (*R*)- and the (*S*)-MTPA derivatives.

<sup>4</sup>) Originally, **6b** crystallized as the piperidinium (*S*)-MTPA salt **6b**·(+)-(*S*)-MTPA. For the sake of simplicity, the carboxylate moiety is omitted in the *Figure*. The full data set is summarized in the *Table* (see *Exper. Part*). CCDC-694216 contains the supplementary crystallographic data for **6b**·(+)-(*S*)-MTPA. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre, via [http://www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).

<sup>5</sup>) H–C(4) is equatorial (*q*-like, <sup>3</sup>*J*(4,3) ≈ <sup>3</sup>*J*(4,5<sub>ax</sub>) ≈ <sup>3</sup>*J*(4,5<sub>eq</sub>) ≈ 3, see *Exper. Part*).

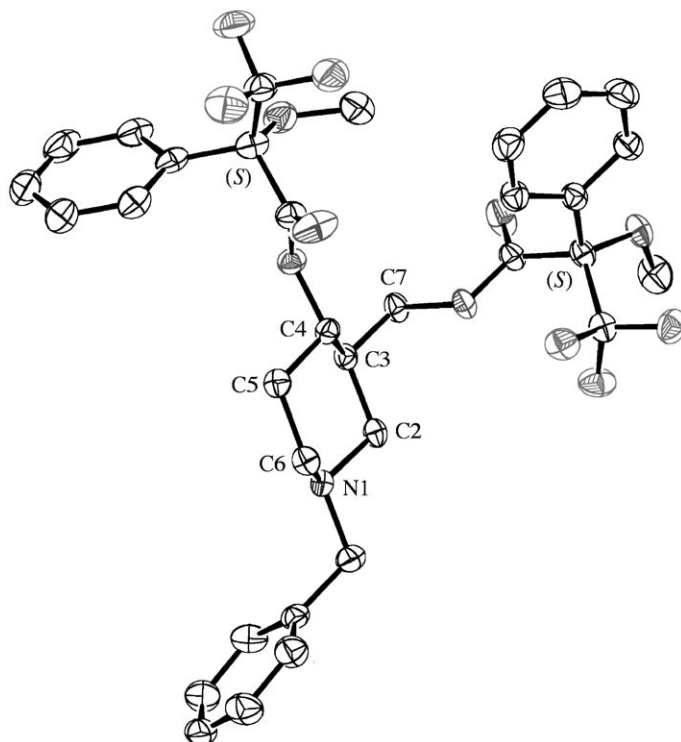


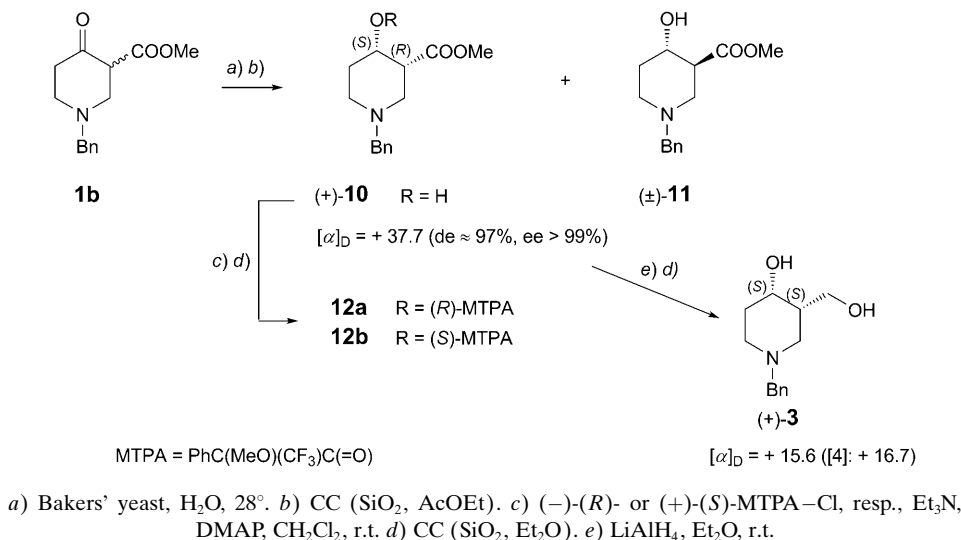
Figure. The molecular structure of **6b**. For reasons of clarity, the systematic atom numbering is restricted to the piperidine part; 50% probability ellipsoids.

The experimental results observed for the couple **8a/8b** ( $\Delta\delta(\text{H}_{\text{ax}}-\text{C}(2), \text{H}_{\text{eq}}-\text{C}(5), \text{and } \text{CH}_2(6)) < 0$  and  $\Delta\delta(\text{H}_{\text{eq}}-\text{C}(2), \text{H}-\text{C}(3), \text{and } \text{H}_{\text{ax}}-\text{C}(5)) > 0$ , and *vice versa* for the couple **9a/9b** see *Exper. Part*)<sup>2</sup>), were in accordance with the prediction. The low quality factor ( $\Delta\delta(\text{H}-\text{C}(4))$ ) reflects the impact of the MTPA–OCH<sub>2</sub> moiety at C(3) and the conformational uncertainty. Taking into account the ambiguity of the differential argumentation, the absolute configurations of the *cis*-4-hydroxypiperidine-3-methanols were tentatively assigned as (+)-(3*S*,4*S*)-**3**, and (–)-(3*R*,4*R*)-**3**. Finally, X-ray crystallographic analyses with direct determinations of the absolute configuration of the (+)- and (–)-*cis*-8-aza-3-phosphadecalins, respectively (*Type II*, *Scheme I*) that were prepared from (+)- and (–)-**3**, fully confirmed the stereochemical assignments made by the unusual application of the *Mosher* method with the bis-MTPA derivatives [4].

2.3. Preparation of (+)-Methyl (3*R*,4*S*)-1-Benzyl-4-hydroxypiperidine-3-carboxylate ((+)-**10**) by Biological Reduction and Chiroptical Correlation with (+)-**3**. According to the protocol [6][7], methyl 1-benzyl-4-oxopiperidine-3-carboxylate hydrochloride (**1b**·HCl) was reduced with bakers' yeast under nonfermenting conditions to afford the dextrorotatory *cis*-4-hydroxy ester (+)-**10** ( $[\alpha]_{\text{D}} = +33.7$ , ee > 99%) as the main product (42%, de > 97%) besides the racemic *trans*-isomer (±)-

**11** (Scheme 3) [8]. Although (+)-**10** turned out to be conformationally very flexible<sup>6)</sup>, the relative *cis*-configuration was established according to the <sup>1</sup>H-NMR multiplicity of H–C(4) that allocates it an equatorial position ( $\delta$  4.10 (*s*-like,  $w_{1/2} \approx 12$  Hz,  $^3J(4,3) \approx ^3J(4,5_{ax}) \approx ^3J(4,5_{eq}) < 3$  Hz)).

Scheme 3



The (4*S*)-configuration was anticipated according to the well investigated stereoselectivity of the NAD(H) dependent oxido reductions [9][10]. Bakers' yeast is a representative of the 'E<sub>3</sub>-type' enzymes [11] that exhibit *pro*-(*R*)-H/*re*-face selectivity and pronounced *cis*-diastereoselectivity in the reduction of  $\alpha$ -substituted cyclic ketones. As a consequence, (+)-**10** is expected to have (3*R*,4*S*)-configuration. A confirmation of this assignment was attempted again by the <sup>1</sup>H-NMR *Mosher* method. Esterification of (+)-**10** with both (+)-(S)- and (–)-(R)-MTPA–Cl afforded the (*R*)-ester **12a**, and the corresponding (*S*)-ester **12b** (Scheme 3) [8]. However, when examining the  $\delta(S) - \delta(R)$  values, all the signals displayed  $\Delta\delta < 0$ , and the relative differences of the magnitudes of  $\Delta\delta$  could not be interpreted straightforwardly. Although  $\Delta\delta(\text{H} - \text{C}(4)) = 0$ , an unambiguous conclusion with respect to the configuration at C(4) was not possible (see *Exper. Part*). This result reflects the unusual conformational flexibility of (+)-**10**<sup>6)</sup> and contrasts with the successful application of the method for the positionally isomeric ethyl 1-benzyl-3-hydroxypiperidine-4-carboxylates [6]. The

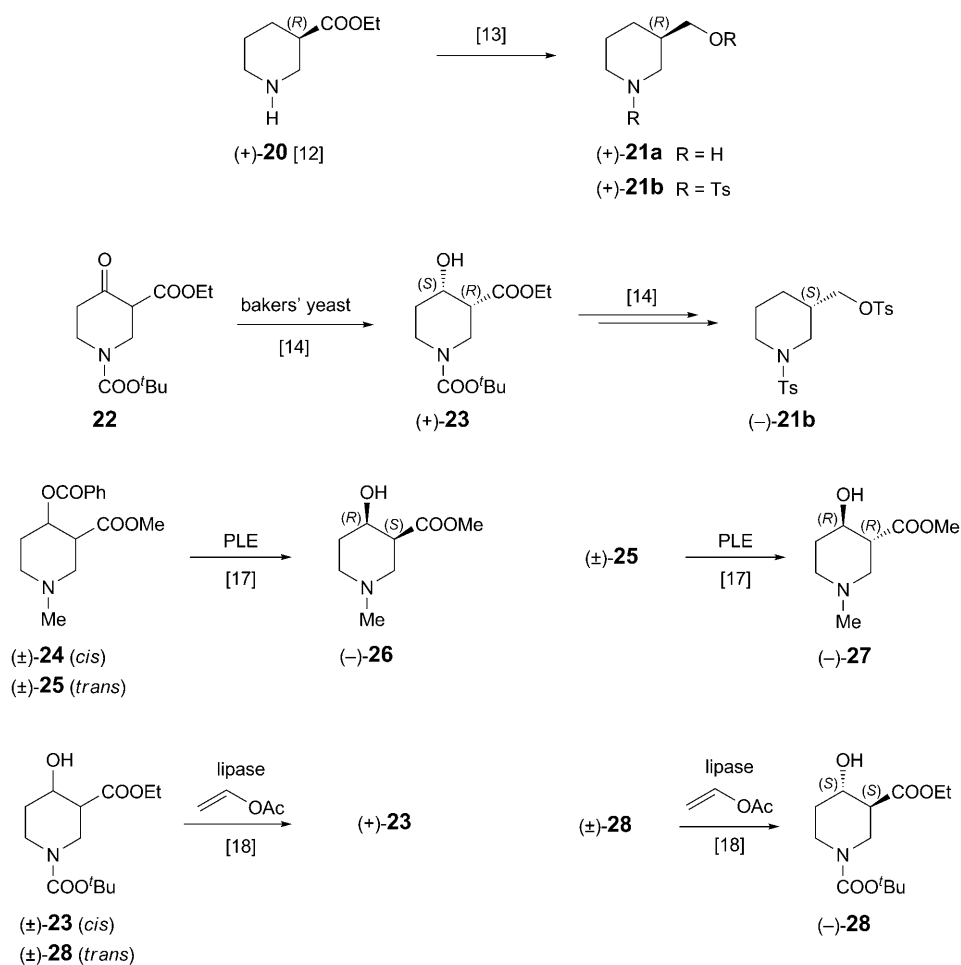
<sup>6)</sup> The conformational flexibility is evidenced in the NMR spectra (see *Exper. Part*): H<sub>ax</sub>–C(2) and H<sub>eq</sub>–C(2) ( $\delta$  2.65 (*m*, *q*-like,  $w_{1/2} \approx 30$  Hz), as well as H<sub>ax</sub>–C(6) and H<sub>eq</sub>–C(6) ( $\delta$  2.49 *m*, (*dt*-like,  $w_{1/2} \approx 40$  Hz) are undistinguishable in the <sup>1</sup>H-NMR. This finding is unprecedented with respect to our observations with related compounds: Usually, H<sub>eq</sub>–C(2) and H<sub>eq</sub>–C(6) are significantly paramagnetically shifted with respect to their axial counterparts [3]. Moreover, the signals of C(2) ( $\delta$  50.7), C(4) ( $\delta$  65.6), and C(6) ( $\delta$  48.7) are broad and hardly exceed the noise in the <sup>13</sup>C-NMR (virtual coalescence).

definite assignment of the absolute configuration at C(4) was effected after reduction of (+)-**10** to (+)-**3**; ( $[\alpha]_D = +15.6$ ) and comparison with authentic (+)-(3*S*,4*S*)-1-benzyl-4-hydroxypiperidine-3-methanol ((+)-**3**,  $[\alpha]_D = +16.7$ , ee > 99%) [4] (*Scheme 3*). Hence, methyl (+)-1-benzyl-4-hydroxypiperidine-3-carboxylate ((+)-**10**) has the (3*R*,4*S*)-configuration. This result confirms the predicted stereochemical outcome of the biological reduction.

**3. Remarks.** 3.1. *The Absolute Configuration of Related 4-Oxypiperidine-3-carboxylates.* The enantiomerically pure 1-benzyl 4-hydroxypiperidine-3-methanols **2** and **3** are not yet described in the literature. But similar investigations are known with related 4-oxy-substituted piperidine-3-carboxylates. To illustrate the inconsistencies mentioned in the introduction, the current knowledge is briefly summarized in the following (*Scheme 4*): The basis of all assignments of the absolute configuration of this series is ethyl (–)-(3*R*)-piperidine-3-carboxylate ((+)-**20**) that has been determined by a modified quadrant rule [12]. Reduction afforded the virtual key compounds, (+)-(3*R*)-piperidine-3-methanol ((+)-**21a**) and the corresponding (+)-(3*R*)-*N,O*-ditosylate (+)-**21b** [13]. Bakers' yeast reduction of 1-(*tert*-butyl) 3-ethyl 4-oxopiperidine-1,3-dicarboxylate (**22**) gave the dextrorotatory *cis*-configured 4-hydroxy ester (+)-**23** (de > 99%, ee > 93%) [14], and chemical transformations yielded the laevorotatory *N,O*-ditosylate (–)-**21b** [14]. Chiroptical correlation led to the assignment of the (3*R*,4*S*)-configuration for (+)-1-(*tert*-butyl) 3-ethyl 4-hydroxypiperidine-1,3-dicarboxylate ((+)-**23**). On the other hand, studies of the reduction of **22** by bakers' yeast reported that the reaction proceeded with very low enantioselectivity [15]. The (3*R*,4*S*)-configuration for the main product (+)-**23** was copied from [14], but the chiroptical data were not consistent<sup>7)</sup> [15]. Ambiguous results have also been described by [17], when a series of piperidin-4-ones with different ester components (Me, Et) and *N*-substituents (Me, CH(Me)<sub>2</sub>, COO<sup>t</sup>Bu) was investigated. The conclusion was that bakers' yeast reduction is not a suitable access for enantiomerically pure piperidines [17]. However, the (±)-*cis*- and (±)-*trans*-methyl 4-(benzoyloxy)-1-methylpiperidine-3-carboxylates ((±)-**24** and (±)-**25**, resp.) could be kinetically resolved by pig-liver esterase (PLE) to afford (–)-methyl (3*S*,4*R*)-4-hydroxy-1-methylpiperidine-3-carboxylate ((–)-**26**; ee 99%) and (–)-methyl (3*R*,4*R*)-4-hydroxy-1-methylpiperidine-3-carboxylate ((–)-**27**; ee 97%) [17]. The absolute configuration of (–)-**26** was assigned chiroptically with reference to its (+)-enantiomer [14] and that of (–)-**27** by an X-ray crystallographic analysis of its 4-{{1-[(4-methylphenyl)sulfonyl]-L-prolyl}oxy} derivative [17]. Recently, lipase-catalyzed acylation of the (±)-*cis*- and (±)-*trans*-1-(*tert*-butyl) 3-ethyl 4-hydroxypiperidine-1,3-dicarboxylates ((±)-**23** and (±)-**28**, resp.) was reported to afford (+)-**23** and (–)-**28**, respectively

<sup>7)</sup> Depending on the reaction conditions,  $[\alpha]_D$  varied from –4 to +23. The same research group reported a reliable result after lipase-catalyzed hydrolysis of 1-(*tert*-butyl) 3,5-dimethyl 4-hydroxypiperidine-1,3,5-tricarboxylate [16], chemical transformations to (+)-*cis*-1-(*tert*-butyl) 3-methyl 4-hydroxypiperidine-1,3-dicarboxylate (ee 79%), and chiroptical correlation referring to [14]. It is noteworthy that the steric course of the desymmetrization was disputed at that time and the assignment of the (3*R*,4*S*)-configuration for the (+)-*cis*-4-hydroxy ester was considered to clear it [16].

Scheme 4



[18]. The (3*R*,4*S*)-configuration for (+)-**23** followed in accordance with [14][17], whereas the (3*S*,4*S*)-configuration for (–)-**28** was guessed on the basis of conclusions by analogy and speculative handling of chiroptical data [18]. The latter is opposite to that determined for the related laevorotatory (–)-methyl 4-hydroxy-1-methylpiperidine-3-carboxylate ((–)-**27**) [17]. However, as electron-withdrawing *N*-substituents can significantly affect the conformation of the piperidine ring<sup>8</sup>), an assignment of the

<sup>8</sup>) Such influences are significant: Due to the partial double-bond character of the C–N carbamate bond [19], *trans*-(*tert*-butyl) 3-hydroxy-2-(hydroxymethyl)piperidine-1-carboxylate adopts the sterically unfavored diaxial conformation [20][21], whereas in the corresponding *trans*-1-benzyl-3-hydroxypiperidine-2-methanol, the diequatorial conformer is predominant as expected [3][21].

absolute configuration from merely the sign of the optical rotation is not applicable<sup>9)</sup>. Hence, it is indispensable to critically check and verify both data and conclusions and, in doubt, to undertake an independent, reliable determination<sup>10)</sup>.

**3.2. Conclusions.** During our work with all stereoisomers of the enantiomerically pure 2-carboxy-3-oxy- [21], 4-carboxy-3-oxy- [6], as well as the present 3-carboxy-4-oxy-disubstituted piperidines, we encountered significant structural inconsistencies. Besides obvious errors (see, *e.g.*, [6]), the most important drawback is that there is no report dealing with a complete set of ‘equal’ compounds (diastereoisomers and enantiomers of the same derivatives, *etc.*), a fact that renders direct, reliable comparisons rather difficult. Moreover, in the majority of cases, isolated reactions of single derivatives under specific reaction conditions have been described, and most of the absolute configurations have been assigned by comparison of the chiroptical data. However, as substituted piperidines are conformationally very flexible, such data are not only determined by the configuration at the stereogenic centers but also significantly by their conformations. In spite of this basic knowledge, most of the assigned absolute configurations have been adopted from precedent articles and lack an independent determination. This is astonishing since piperidine-based compounds are pharmaceutically most promising key substances, and the correctness of their structure is an indispensable prerequisite – not only from the scientific viewpoint but also with respect to medical applications and legal aspects connected therewith.

We thank PD Dr. A. Linden, head of the X-ray department of our institute, for the X-ray crystallographic analysis. The financial support of the project by the *Swiss National Foundation* is gratefully acknowledged.

### Experimental Part

1. *General.* See [1][3]. Anal. HPLC: the retention is expressed by the capacity ratio  $k' = (t_R - t_0)/t_0$ , with  $t_R$  = retention time and  $t_0$  = column dead time (elution time of an unretained component);  $\alpha$  = separation factor,  $R_s$  = resolution.  $[\alpha]_D^{25}$ : Perkin-Elmer 241-MC polarimeter with thermostat B. Braun Thermomix 1441; 10 cm cell; in acetone,  $c = 1$ ; ee by integration of the peak areas of the anal. HPLC separations with optimized resolution ( $R_s > 4$ ) and high sensitivity. <sup>1</sup>H-NMR: all assignments of strongly overlapping <sup>1</sup>H-signals by 2D experiments.

2. (+)-(3R,4S)- and (-)-(3S,4R)-, and (+)-(3S,4S)- and (-)-(3R,4R)-1-Benzyl-4-hydroxypiperidine-3-methanols ((+)- and (-)-**2**, and (+)- and (-)-**3**, resp.). 2.1. *Ethyl and Methyl 1-Benzyl-4-oxopiperidine-3-carboxylates* (**1a** and **1b**, resp.). The starting piperidin-4-ones were prepared by Dieckmann condensation of diethyl or dimethyl 3,3'-(benzylimino)bis[propanoate] (= *N*-(3-methoxy- or -3-ethoxypropyl)-*N*-(phenylmethyl)- $\beta$ -alanine methyl or ethyl ester), resp. (obtained after benzylation of ethyl or methyl 3-bromopropanoate, resp.) by standard procedures [4][8].

2.2. 6-Benzylhexahydro-2,2-dimethyl-4H-1,3-dioxino[5,4-*c*]pyridines ( $\pm$ )-**4** and ( $\pm$ )-**5** and HPLC Separation of the Enantiomers. The acetonides ( $\pm$ )-**4** and ( $\pm$ )-**5** were prepared from **1a** according to [3].

<sup>9)</sup> Although we had shown in the isomeric 3-hydroxypiperidine-1,4-dicarboxylate [6] and in the 3-hydroxypiperidine-1,2-dicarboxylate [21] series that the transformation of their carbamate moiety including N(1) into the corresponding 1-benzyl derivative only affected the magnitude of the optical rotation but did not change its sign, these particular findings cannot be generalized.

<sup>10)</sup> An example illustrating the consequences when data are uncritically copied is the incorrect assignment of the (3S,4S)-configuration for the isomeric (+)-1-(*tert*-butyl) 4-ethyl 3-hydroxypiperidine-1,4-dicarboxylate (instead of (+)-(3R,4R) [6]) [14]. It has been adopted in subsequent investigations by other authors (*e.g.*, [18]) and has led to further misinterpretations.

Anal. HPLC of the racemic mixtures (*Chiralcel*<sup>®</sup> OD-*H*, hexane/EtOH 600 : 1): (–)-**4** ( $k' = 2.22$ ) and (+)-**4** ( $k' = 2.60$ ) with  $\alpha = 1.17$  and  $R_s = 2.4$ ; (+)-**5** ( $k' = 2.00$ ) and (–)-**5** ( $k' = 3.11$ ) with  $\alpha = 1.56$  and  $R_s = 5.8$ . Anal. HPLC (*Chiralcel*<sup>®</sup> OD-*H*, hexane/EtOH 2000 : 1): (–)-**4** ( $k' = 5.99$ ) and (+)-**4** ( $k' = 8.04$ ) with  $\alpha = 1.34$  and  $R_s = 4.4$ ; (+)-**5** ( $k' = 4.14$ ) and (–)-**5** ( $k' = 6.39$ ) with  $\alpha = 1.54$  and  $R_s = 4.2$ . Prep. HPLC (*Chiralcel*<sup>®</sup> OD, hexane/EtOH 2000 : 1) of (±)-**4** (3.45 g) and recrystallization from hexane afforded (+)-**4** (890 mg) and (–)-**4** (655 mg) as colorless crystals. Prep. HPLC (*Chiralcel*<sup>®</sup> OD, hexane/EtOH 600 : 1) of (±)-**5** (2.72 g) and purification by CC (SiO<sub>2</sub>, Et<sub>2</sub>O) gave (+)-**5** (885 mg) and (–)-**5** (600 mg) as colorless crystals.

Data of (+)-**4**:  $R_f$  (hexane/Et<sub>2</sub>O 1 : 1) 0.25. M.p. 62–63°.  $[\alpha]_D = +29.2$  (ee > 99%). All other data: identical with those of (±)-**4** [3].

Data of (–)-**4**:  $[\alpha]_D = -29.3$  (ee > 99%),  $[\alpha]_D = -28.7$  (ee > 98%)<sup>1</sup>. All other data: identical with those of (+)-**4**.

Data of (+)-**5**:  $R_f$  (hexane/Et<sub>2</sub>O 1 : 1) 0.04. M.p. 47–48°.  $[\alpha]_D = +66.1$  (ee > 99%). All other data: identical with those of (±)-**5** [3].

Data of (–)-**5**:  $[\alpha]_D = -66.5$  (ee > 99%). All other data: identical with those of (+)-**5**.

2.3. *1-Benzyl-4-hydroxypiperidine-3-methanols 2 and 3*. Hydrolysis of **4** and **5** was performed by suspending each enantiomer in H<sub>2</sub>O/1*N* HCl 1 : 1 (2 ml) and stirring at 60° for 2 h (TLC control). Workup afforded the piperidine-3-methanols as colorless oils (ca. 100%) that solidified in the refrigerator. Products: (+)-**4** (120 mg) → (–)-**2** (101 mg), (–)-**4** (140 mg) → (+)-**2** (118 mg), (+)-**5** (130 mg) → (+)-**3** (109 mg), and (–)-**5** (110 mg) → (–)-**3** (93 mg).

Data of (+)-**2**:  $R_f$  (Et<sub>2</sub>O) 0.01. M.p. 69–71°.  $[\alpha]_D = +9.2$  (ee > 98%)<sup>1</sup>. All other data: identical with those of (±)-**2** [3].

Data of (–)-**2**:  $[\alpha]_D = -9.8$  (ee > 99%). All other data: identical with those of (+)-**2**.

Data of (+)-**3**:  $R_f$  (Et<sub>2</sub>O) 0.01. M.p. 134–135°.  $[\alpha]_D = +16.7$  (ee > 99%). All other data: identical with those of (±)-**3** [3].

Data of (–)-**3**:  $[\alpha]_D = -16.6$  (ee > 99%). All other data: identical with those of (+)-**3**.

3. (*R*)- and (*S*)-MTPA Derivatives for the Determination of the Absolute Configuration of (+)- and (–)-**2** and (+)- and (–)-**3**. To the soln. of the diols (+)- or (–)-**2**, or (+)- or (–)-**3** (each 15 mg, 0.07 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (3 ml), Et<sub>3</sub>N (33  $\mu$ l, 0.22 mmol) and DMAP (2 mg) were added, and the mixture was treated with (+)-(*S*)-MTPA–Cl (30  $\mu$ l, 0.16 mmol, 2.3 equiv.) at r.t. for 16 h. The mixture was poured onto ice-H<sub>2</sub>O and thoroughly washed with 0.01*N* HCl and sat. NaCl soln. Evaporation of the org. solvent and chromatographic purification (SiO<sub>2</sub>, AcOEt) of the crude products afforded the (*R*)-MTPA diesters **6a–9a**. Analogously, (+)- or (–)-**2** and (+)- or (–)-**3** were treated with (–)-(*R*)-MTPA–Cl to yield the (*S*)-MTPA diesters **6b–9b**. All MTPA derivatives were isolated in pure form as colorless, viscous oils: **6a** (38.9 mg, 89%), **6b** (35.9 mg, 82%), **7a** (35.4 mg, 81%), **7b** (35.9 mg, 82%), **8a** (38.1 mg, 87%), **8b** (39.4 mg, 90%), **9a** (40.5 mg, 92%), and **9b** (35.1 mg, 80%). The fraction containing **6b** solidified at ca. –20° to form colorless prisms (from *i*-PrOH) of **6b**·(+)-(*S*)-MTPA, m.p. 20–25°, suitable for an X-ray crystallographic analysis (see Fig. and Table below).

Data of the (*R*)- and (*S*)-MTPA Diesters **6a** and **6b** of (+)-**2**. {(*3R,4S*)-1-Benzyl-4-[(2*R*)-3,3,3-trifluoro-2-methoxy-1-oxo-2-phenylpropoxy]piperidin-3-yl)methyl ( $\alpha$ R)- $\alpha$ -Methoxy- $\alpha$ -(trifluoromethyl)-benzeneacetate (bis-(*R*)-MTPA ester **6a**): <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>): 7.50–7.43, 7.34–7.34 (2*m*, 2 Ph); 7.33–7.24 (*m*, PhCH<sub>2</sub>); 4.80 (*td*, <sup>3</sup>*J*(4,3) = <sup>3</sup>*J*(4,5<sub>ax</sub>) = 10.2, <sup>3</sup>*J*(4,5<sub>eq</sub>) = 4.5, H–C(4)); 4.13, 4.05 (each *dd*, <sup>2</sup>*J* = 11.8, <sup>3</sup>*J* = 5.1, <sup>3</sup>*J* = 2.6, CH<sub>2</sub>(OMTPA)); 3.63, 3.40 (*AB*, <sup>2</sup>*J* = 13.2, PhCH<sub>2</sub>); 3.52, 3.45 (each *s*, MeO); 2.98 (*br. t*-like, *w*<sub>1/2</sub> ≈ 30, H<sub>eq</sub>–C(2), H<sub>eq</sub>–C(6)); 2.31 (*oct*-like, *w*<sub>1/2</sub> ≈ 22, H–C(3)); 2.22 (*m, br. td*-like, *w*<sub>1/2</sub> ≈ 18, H<sub>eq</sub>–C(5), H<sub>ax</sub>–C(6)); 2.08 (*t*, <sup>2</sup>*J* = <sup>3</sup>*J*(2<sub>ax</sub>,3) ≈ 11, H<sub>ax</sub>–C(2)); 1.86 (*br. qd*-like, <sup>2</sup>*J* = 12.8, <sup>3</sup>*J*(5<sub>ax</sub>,4) = 10.2, <sup>3</sup>*J*(5<sub>ax</sub>,6<sub>ax</sub>) = 11.2, <sup>3</sup>*J*(5<sub>ax</sub>,6<sub>eq</sub>) = 3.8, H<sub>ax</sub>–C(5)). <sup>13</sup>C-NMR (125.8 MHz, CDCl<sub>3</sub>): 166.3, 165.9 (CO of MTPA); 137.4 (C(1')); 132.4, 132.2 (C(1''), C(1''')); 129.9 (C(4''), C(4''')); 129.7 (C(2'), C(6')); 128.8, (C(2''), C(6''), C(2'''), C(6''')); 128.7 (C(3'), C(5')); 127.5 (C(3''), C(5''), C(5''')); 127.2 (C(4')); 123.5 (*q*, <sup>1</sup>*J*(C,F) = 289, 2 CF<sub>3</sub>); 84.8, 84.6 (each *q*, <sup>2</sup>*J*(C,F) = 28.3, PhC(MeO)(CF<sub>3</sub>)C(=O)); 72.3 (C(4)); 64.0 (CH<sub>2</sub>(OMTPA)); 61.9 (PhCH<sub>2</sub>); 55.6, 55.5 (2 MeO); 53.2 (C(2)); 50.6 (C(6)); 39.4 (C(3)); 29.3 (C(5)).

{(*3R,4S*)-1-Benzyl-4-[(2*S*)-3,3,3-trifluoro-2-methoxy-1-oxo-2-phenylpropoxy]piperidin-3-yl)methyl ( $\alpha$ S)- $\alpha$ -Methoxy- $\alpha$ -(trifluoromethyl)benzeneacetate (bis-(*S*)-MTPA ester **6b**): <sup>1</sup>H-NMR (500 MHz,

$\text{CDCl}_3$ ): 7.47–7.22 (*m*, 2 Ph,  $\text{PhCH}_2$ ); 4.81 (*sext*-like,  $\text{H}-\text{C}(4)$ ); 4.81 (*td*,  $^3J(4,3) = ^3J(4,5_{\text{ax}}) = 9.8$ ,  $^3J(4,5_{\text{eq}}) = 4.2$ ,  $\text{H}-\text{C}(4)$ ); 4.13 (*td*-like,  $^2J = 12$ ,  $^3J \approx 5$ ,  $^3J \approx 3$ ,  $\text{CH}_2(\text{OMTPA})$ ); 3.81, 3.76 (*AB*,  $^2J = 13.2$ ,  $\text{PhCH}_2$ ); 3.45, 3.44 (each *s*, 2 MeO); 3.19 (br. *s*-like,  $w_{1/2} \approx 20$ ,  $\text{H}_{\text{eq}}-\text{C}(6)$ ); 3.10 (br. *d*,  $^2J = 11$ ,  $w_{1/2} \approx 20$ ,  $\text{H}_{\text{eq}}-\text{C}(2)$ ); 2.45 (*m*,  $w_{1/2} \approx 18$ ,  $\text{H}-\text{C}(3)$ ); 2.35 (br. *t*,  $^2J \approx ^3J(6_{\text{ax}}, 5_{\text{ax}}) \approx 12$ ,  $^3J(6_{\text{ax}}, 5_{\text{eq}})$  not resolved,  $\text{H}_{\text{ax}}-\text{C}(6)$ ); 2.23 (*t*,  $^2J \approx ^3J(2_{\text{ax}}, 3) \approx 11.5$ ,  $\text{H}_{\text{ax}}-\text{C}(2)$ ); 2.19 (*dq*-like,  $^2J = 11$ ,  $^3J(5_{\text{eq}}, 4) \approx ^3J(5_{\text{eq}}, 6_{\text{ax}}) \approx ^3J(5_{\text{eq}}, 6_{\text{eq}}) \approx 4$ ,  $\text{H}_{\text{eq}}-\text{C}(5)$ ); 1.84 (br. *qd*-like,  $^2J = 13.5$ ,  $^3J(5_{\text{ax}}, 4) = 9.8$ ,  $^3J(5_{\text{ax}}, 6_{\text{ax}}) = 11.5$ ,  $^3J(5_{\text{ax}}, 6_{\text{eq}}) \approx 4$ ,  $\text{H}_{\text{ax}}-\text{C}(5)$ ).  $^{13}\text{C}$ -NMR (125.8 MHz,  $\text{CDCl}_3$ ): 166.3, 166.2 (CO of MTPA); 135.0 ( $\text{C}(1')$ ); 132.0, 131.8 ( $\text{C}(1'')$ ,  $\text{C}(1''')$ ); 130.4 ( $\text{C}(2')$ ,  $\text{C}(6')$ ); 130.1 ( $\text{C}(4'')$ ,  $\text{C}(4''')$ ); 129.1 ( $\text{C}(3')$ ,  $\text{C}(5')$ ); 128.9, 128.8 ( $\text{C}(2'')$ ,  $\text{C}(6'')$ ,  $\text{C}(2''')$ ,  $\text{C}(6''')$ ); 127.7 ( $\text{C}(4')$ ); 127.4 ( $\text{C}(3'')$ ,  $\text{C}(5'')$ ,  $\text{C}(3''')$ ,  $\text{C}(5''')$ ); 123.5, 123.4 (each *q*,  $^1J(\text{C}, \text{F}) = 289$ ,  $\text{CF}_3$ ); 85.0, 84.9 (each *q*,  $^2J(\text{C}, \text{F}) = 28.1$ ,  $\text{PhC}(\text{MeO})(\text{CF}_3)\text{C}(=\text{O})$ ); 71.3 ( $\text{C}(4)$ ); 63.5 ( $\text{CH}_2(\text{OMTPA})$ ); 61.2 ( $\text{PhCH}_2$ ); 55.6, 55.5 (2 MeO); 52.2 ( $\text{C}(2)$ ); 50.0 ( $\text{C}(6)$ ); 38.5 ( $\text{C}(3)$ ); 28.2 ( $\text{C}(5)$ ).

$\Delta\delta(^1\text{H}) = \delta(S) - \delta(R)$  (in Hz):  $\text{H}-\text{C}(4)$ , +5<sup>3</sup>;  $\text{H}_{\text{ax}}-\text{C}(2)$ , +75;  $\text{H}_{\text{eq}}-\text{C}(2)$ , +60;  $\text{H}-\text{C}(3)$ , +70;  $\text{H}_{\text{ax}}-\text{C}(5)$ , -10;  $\text{H}_{\text{eq}}-\text{C}(5)$ , -15  $\rightarrow$  (4*S*)-configuration.

**Data of the (R)- and (S)-MTPA Diesters 7a and 7b of (-)-2.** Being enantiomeric compounds, **7a** and **6b** (**7a** = *ent*-**6b**) as well as **7b** and **6a** (**7b** = *ent*-**6a**) exhibited identical NMR spectra, only the sign of  $\Delta\delta$  is inverted:  $\Delta\delta(^1\text{H}) = \delta(S) - \delta(R)$  (in Hz):  $\text{H}-\text{C}(4)$ , +5<sup>3</sup>;  $\text{H}_{\text{ax}}-\text{C}(2)$ , -75;  $\text{H}_{\text{eq}}-\text{C}(2)$ , -60;  $\text{H}-\text{C}(3)$ , -70;  $\text{H}_{\text{ax}}-\text{C}(5)$ , +10;  $\text{H}_{\text{eq}}-\text{C}(5)$ , +15  $\rightarrow$  (4*R*)-configuration.

**Data of the (R)- and (S)-MTPA Diesters 8a and 8b of (+)-3.** *[(3*S*,4*S*)-1-Benzyl-4-[(2*R*)-3,3,3-trifluoro-2-methoxy-1-oxo-2-phenylpropoxy]piperidin-3-yl]methyl (α*R*)-α-Methoxy-α-(trifluoromethyl)benzeneacetate* (bis-(*R*)-MTPA ester **8a**):  $^1\text{H}$ -NMR (500 MHz,  $\text{CDCl}_3$ ): 7.51–7.48, 7.47–7.34 (2*m*, 2 Ph); 7.32–7.23 (*m*,  $\text{PhCH}_2$ ); 5.25 (*q*-like,  $^3J(4,3) \approx ^3J(4,5_{\text{ax}}) \approx ^3J(4,5_{\text{eq}}) \approx 3$ ,  $\text{H}-\text{C}(4)$ ); 4.09 (*m*,  $w_{1/2} \approx 22$ ), 4.02 (*dd*,  $^2J = 11.0$ ,  $^3J = 6.8$ ,  $\text{CH}_2(\text{OMTPA})$ ); 3.51, 3.45 (*AB*,  $^2J = 13.2$ ,  $\text{PhCH}_2$ ); 3.50, 3.42 (each *q*,  $^3J(\text{Me}, \text{F}) = 1.1$ , 2 MeO); 2.64 (*m*,  $w_{1/2} \approx 22$ ,  $\text{H}_{\text{eq}}-\text{C}(6)$ ); 2.55 (br. *d*,  $^2J = 10$ ,  $w_{1/2} \approx 22$ ,  $\text{H}_{\text{eq}}-\text{C}(2)$ ); 2.35 (*m*,  $w_{1/2} \approx 25$ ,  $\text{H}-\text{C}(3)$ ); 2.26 (*m*,  $w_{1/2} \approx 30$ ,  $\text{H}_{\text{ax}}-\text{C}(6)$ ); 2.14 (*m*,  $w_{1/2} \approx 30$ ,  $\text{H}_{\text{ax}}-\text{C}(2)$ ); 1.93 (br. *dq*-like,  $\text{H}_{\text{ax}}-\text{C}(5)$ ); 1.92 (*m*, br. *t*-like,  $\text{H}_{\text{eq}}-\text{C}(5)$ ).  $^{13}\text{C}$ -NMR (125.8 MHz,  $\text{CDCl}_3$ ): 166.8, 166.1 (CO of MTPA); 138.8 ( $\text{C}(1')$ ); 132.8, 132.6 ( $\text{C}(1'')$ ,  $\text{C}(1''')$ ); 130.21, 130.17 ( $\text{C}(4'')$ ,  $\text{C}(4''')$ ); 129.5 ( $\text{C}(2')$ ,  $\text{C}(6')$ ); 129.1, 129.0 ( $\text{C}(2'')$ ,  $\text{C}(6'')$ ,  $\text{C}(2''')$ ,  $\text{C}(6''')$ ); 128.9 ( $\text{C}(3')$ ,  $\text{C}(5')$ ); 127.9 ( $\text{C}(4')$ ); 127.7 ( $\text{C}(3'')$ ,  $\text{C}(5'')$ ,  $\text{C}(3''')$ ,  $\text{C}(5''')$ ); 123.9, 123.7 (each *q*,  $^1J(\text{C}, \text{F}) = 288$ ,  $\text{CF}_3$ ); 85.1, 85.0 (each *q*,  $^2J(\text{C}, \text{F}) = 27.6$ ,  $\text{PhC}(\text{OMe})(\text{CF}_3)\text{C}(=\text{O})$ ); 71.3 ( $\text{C}(4)$ ); 64.7 ( $\text{CH}_2(\text{OMTPA})$ ); 63.2 ( $\text{PhCH}_2$ ); 55.9 (2 MeO); 51.1 ( $\text{C}(2)$ ); 48.3 ( $\text{C}(6)$ ); 39.2 ( $\text{C}(3)$ ); 29.6 ( $\text{C}(5)$ ).

*[(3*S*,4*S*)-1-Benzyl-4-[(2*S*)-3,3,3-trifluoro-2-methoxy-1-oxo-2-phenylpropoxy]piperidin-3-yl]methyl (α*S*)-α-Methoxy-α-(trifluoromethyl)benzeneacetate* (bis-(*S*)-MTPA ester **8b**):  $^1\text{H}$ -NMR (500 MHz,  $\text{CDCl}_3$ ): 7.48–7.43, 7.42–7.34 (2*m*, 2 Ph); 7.31–7.21 (*m*,  $\text{PhCH}_2$ ); 5.18 (*q*-like,  $^3J(4,3) \approx ^3J(4,5_{\text{ax}}) \approx ^3J(4,5_{\text{eq}}) \approx 3$ ,  $\text{H}-\text{C}(4)$ ); 4.09 (*m*,  $w_{1/2} \approx 24$ ), 4.05 (*dd*,  $^2J = 11.0$ ,  $^3J = 7.9$ ,  $\text{CH}_2(\text{OMTPA})$ ); 3.47, 3.40 (*AB*,  $^2J = 13.2$ ,  $\text{PhCH}_2$ ); 3.47, 3.44 (each *q*,  $^3J(\text{Me}, \text{F}) = 1.0$ , 2 MeO); 2.56 (br. *t*-like,  $w_{1/2} \approx 25$ ,  $\text{H}_{\text{eq}}-\text{C}(2)$ ,  $\text{H}_{\text{eq}}-\text{C}(6)$ ); 2.36 (*m*,  $w_{1/2} \approx 22$ ,  $\text{H}-\text{C}(3)$ ); 2.09 (br. *t*-like,  $w_{1/2} \approx 50$ ,  $\text{H}_{\text{ax}}-\text{C}(2)$ ,  $\text{H}_{\text{ax}}-\text{C}(6)$ ); 1.96 (br. *dq*-like,  $^2J \approx 12$ ,  $w_{1/2} \approx 24$ ,  $\text{H}_{\text{ax}}-\text{C}(5)$ ); 1.86 (br. *t*-like,  $^2J \approx 12$ ,  $w_{1/2} \approx 24$ ,  $\text{H}_{\text{eq}}-\text{C}(5)$ ).  $^{13}\text{C}$ -NMR (125.8 MHz,  $\text{CDCl}_3$ ): 166.6, 165.9 (CO of MTPA); 137.7 ( $\text{C}(1')$ ); 132.2, 131.2 ( $\text{C}(1'')$ ,  $\text{C}(1''')$ ); 130.0, 129.9 ( $\text{C}(4'')$ ,  $\text{C}(4''')$ ); 129.3 ( $\text{C}(2')$ ,  $\text{C}(6')$ ); 128.8, 128.7 ( $\text{C}(2'')$ ,  $\text{C}(6'')$ ,  $\text{C}(2''')$ ,  $\text{C}(6''')$ ); 128.6 ( $\text{C}(3')$ ,  $\text{C}(5')$ ); 127.6 ( $\text{C}(3'')$ ,  $\text{C}(5'')$ ,  $\text{C}(3''')$ ,  $\text{C}(5''')$ ); 127.4 ( $\text{C}(4')$ ); 123.6, 123.4 (each *q*,  $^1J(\text{C}, \text{F}) = 289$ ,  $\text{CF}_3$ ); 85.0, 84.8 (each *q*,  $^2J(\text{C}, \text{F}) = 27.9$ ,  $\text{PhC}(\text{OMe})(\text{CF}_3)\text{C}(=\text{O})$ ); 70.9 ( $\text{C}(7)$ ); 64.6 ( $\text{C}(7)$ ); 62.9 ( $\text{PhCH}_2$ ); 55.6, 55.5 (2 MeO); 50.5 ( $\text{C}(2)$ ); 48.3 ( $\text{C}(6)$ ); 38.8 ( $\text{C}(3)$ ); 29.1 ( $\text{C}(5)$ ).

$\Delta\delta(^1\text{H}) = \delta(S) - \delta(R)$  (in Hz):  $\text{H}-\text{C}(4)$ , -35<sup>3</sup>;  $\text{H}_{\text{ax}}-\text{C}(2)$ , -25;  $\text{H}_{\text{eq}}-\text{C}(2)$ , +5;  $\text{H}-\text{C}(3)$ , +5;  $\text{H}_{\text{ax}}-\text{C}(5)$ , +15;  $\text{H}_{\text{eq}}-\text{C}(5)$ , -30;  $\text{H}_{\text{ax}}-\text{C}(6)$ , -85;  $\text{H}_{\text{eq}}-\text{C}(6)$ , -40  $\rightarrow$  (4*S*)-configuration.

**Data of the (R)- and (S)-MTPA Diesters 9a and 9b of (-)-3.** Being enantiomeric compounds, **9a** and **8b** (**9a** = *ent*-**8b**) as well as **9b** and **8a** (**9b** = *ent*-**8a**) exhibited identical NMR spectra, only the sign of  $\Delta\delta$  is inverted:  $\Delta\delta(^1\text{H}) = \delta(S) - \delta(R)$  (in Hz):  $\text{H}-\text{C}(4)$ , +35<sup>3</sup>;  $\text{H}_{\text{ax}}-\text{C}(2)$ , +25;  $\text{H}_{\text{eq}}-\text{C}(2)$ , -5;  $\text{H}-\text{C}(3)$ , -5;  $\text{H}_{\text{ax}}-\text{C}(5)$ , -15;  $\text{H}_{\text{eq}}-\text{C}(5)$ , +30;  $\text{H}_{\text{ax}}-\text{C}(6)$ , +85;  $\text{H}_{\text{eq}}-\text{C}(6)$ , +40  $\rightarrow$  (4*R*)-configuration.

4. (+)-Methyl (3*R*,4*S*)-1-Benzyl-4-hydroxypiperidine-3-carboxylate ((+)-**10**). 4.1. Methyl (±)-cis- and Methyl (±)-trans-1-Benzyl-4-hydroxypiperidine-3-carboxylates ((±)-**10** and (±)-**11**, resp.). To a cooled soln. of ethyl 1-benzyl-4-oxopiperidine-3-carboxylate hydrochloride (**1a**·HCl; 1.01 g, 3.4 mmol) and anh.  $\text{Na}_2\text{CO}_3$  (540 mg, 5.1 mmol) in MeOH (50 ml),  $\text{NaBH}_4$  (60 mg, 1.7 mmol) was added in portions

and the mixture stirred at  $-15^{\circ}$ . To complete the transesterification, the mixture was kept at  $30^{\circ}$  for 2 h. Workup and continuous extraction with  $\text{Et}_2\text{O}$  yielded the mixture of the crude 4-hydroxy esters ( $\pm$ )-**10**/( $\pm$ )-**11** (585 mg, 69%). Separation of the diastereoisomers (200 mg) by CC ( $\text{SiO}_2$ , hexane/ $\text{AcOEt}$  20:1) gave ( $\pm$ )-**11** (60 mg) and from the more polar fraction ( $\pm$ )-**10** (30 mg), both as colorless viscous oils. Anal. HPLC of the racemic mixture (*Chiralcel*<sup>®</sup> OD-H, hexane/*sec*-BuOH 60:1): (+)-**10** ( $k' = 9.1$ ) and (–)-**10** ( $k' = 10.9$ ) with  $\alpha = 1.20$  and  $R_S > 4$ ; ( $\pm$ )-**11** ( $k' = 12.7$  and  $13.8$ ) with  $\alpha = 1.09$  and  $R_S = 1.3$ .

Data of ( $\pm$ )-**10**:  $R_f$  (hexane/ $\text{AcOEt}$  1:19) 0.15. IR (film): 3434m, 2949m, 2824m, 1736vs, 1659w, 1494w, 1454m, 1436m, 1360m, 1295m, 1204s, 1125m, 1073m, 1056m, 1027m, 979m, 919w, 856w, 797w, 743m, 699s.  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ ): 7.31–7.21 (m,  $\text{PhCH}_2$ ); 4.10 (s-like,  $w_{1/2} \approx 12$ , H–C(4)); 3.68 (s, MeO); 3.56, 3.49 (AB,  $^2J = 13.2$   $\text{PhCH}_2$ ); 2.77 (m, *quint*-like,  $w_{1/2} \approx 15$ , H–C(3)); 2.65 (m, *q*-like,  $w_{1/2} \approx 30$ ,  $\text{CH}_2(2)$ ); 2.49 (m, *dt*-like,  $w_{1/2} \approx 40$ ,  $\text{CH}_2(6)$ ); 1.87, 1.79 (each *ddd*-like,  $^2J = 13.5$ ,  $^3J = 3.5$ , 4.5, 5.0,  $\text{CH}_2(5)$ ).  $^{13}\text{C-NMR}$  (125.8 MHz,  $\text{CDCl}_3$ ): 174.2 (COOMe); 138.4 (C(1')); 129.0 (C(2'), C(6')); 128.2 (C(3'), C(5')); 127.1 (C(4')); 65.6 (br. (C(4))<sup>6</sup>); 62.8 ( $\text{PhCH}_2$ ); 51.7 (MeO); 50.7 (br. (C(2))<sup>6</sup>); 48.7 (br. (C(6))<sup>6</sup>); 46.5 (C(3)); 31.9 (C(5)). EI-MS: 249 (8,  $M^+$ ), 231 (15,  $[M - \text{H}_2\text{O}]^+$ ), 218 (3), 190 (9), 170 (8), 158 (25), 140 (17), 132 (10), 120 (8), 91 (100,  $\text{PhCH}_2^+$ ), 65 (11), 55 (2).

Data of ( $\pm$ )-**11**:  $R_f$  (hexane/ $\text{AcOEt}$  1:19) 0.23. IR (film): 3434m, 3062w, 2949m, 2823m, 1736vs, 1656w, 1495w, 1453m, 1437m, 1360m, 1296m, 1204s, 1126m, 1095m, 1073m, 1055m, 1027m, 979m, 918w, 856w, 796w, 742m, 799s.  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ ): 7.34–7.23 (m,  $\text{PhCH}_2$ ); 3.80 (br. *tt*-like,  $^3J(4,5_{\text{ax}}) \approx 12$ ,  $^3J(4,3) = 11.5$ ,  $^3J(4,5_{\text{eq}}) \approx 5$ ,  $^3J(4,\text{OH}) = 3.2$ , H–C(4)); 3.70 (s, MeO); 3.54 (s,  $\text{PhCH}_2$ ); 3.13 (*ddd*,  $^2J = 11.5$ ,  $^3J(2_{\text{eq}},3) = 4.0$ ,  $^4J(2_{\text{eq}},6_{\text{eq}}) = 2.2$ ,  $\text{H}_{\text{eq}}\text{--C}(2)$ ); 2.98 (d,  $^3J(\text{OH},4) = 3.2$ , OH–C(4)); 2.89 (br. *dt*-like,  $^2J \approx 12$ ,  $^3J(6_{\text{eq}},5_{\text{ax}}) \approx 4$ ,  $^3J(6_{\text{eq}},5_{\text{eq}}) \approx 3$ ,  $^4J(6_{\text{eq}},2_{\text{eq}}) = 2.2$ ,  $\text{H}_{\text{eq}}\text{--C}(6)$ ); 2.63 (*td*,  $^3J(3,4) = ^3J(3,2_{\text{ax}}) = 11.5$ ,  $^3J(3,2_{\text{eq}}) \approx 4$ , H–C(3)); 2.08 (t,  $^2J = ^3J(2_{\text{ax}},3) = 11.5$ ,  $\text{H}_{\text{ax}}\text{--C}(2)$ ); 2.07 (br. *td*,  $^2J \approx ^3J(6_{\text{ax}},5_{\text{ax}}) \approx 12$ ,  $^3J(6_{\text{ax}},5_{\text{eq}}) \approx 2.5$ ,  $\text{H}_{\text{ax}}\text{--C}(6)$ ); 1.96 (br. *ddd*,  $^2J \approx 12$ ,  $^3J(\text{eq},4) \approx 5$ ,  $^3J(5_{\text{eq}},6_{\text{eq}}) \approx 3$ ,  $^3J(5_{\text{eq}},6_{\text{ax}}) \approx 2.5$ ,  $\text{H}_{\text{eq}}\text{--C}(5)$ ); 1.65 (br. *qd*,  $^2J \approx ^3J(5_{\text{ax}},4) \approx ^3J(5_{\text{ax}},6_{\text{ax}}) \approx 12$ ,  $^3J(5_{\text{ax}},6_{\text{eq}}) \approx 4$ ,  $\text{H}_{\text{ax}}\text{--C}(5)$ ).  $^{13}\text{C-NMR}$  (125.8 MHz,  $\text{CDCl}_3$ ): 172.1 (COOMe); 136.1 (C(1')); 126.8 (C(2'), C(6')); 126.1 (C(3'), C(5')); 125.0 (C(4')); 67.5 (C(4)); 60.1 ( $\text{PhCH}_2$ ); 51.1 (MeO); 49.8 (C(2)); 49.3 (C(6)); 47.4 (C(3)); 30.5 (C(5)). EI-MS: 249 (7,  $M^+$ ), 231 (1,  $[M - \text{H}_2\text{O}]^+$ ), 218 (4), 190 (10), 172 (7), 158 (22), 140 (17), 120 (10), 91 (100,  $\text{PhCH}_2^+$ ), 82 (4), 65 (9), 55 (8).

4.2. Reduction of **1b** with Bakers' Yeast. Methyl 1-benzyl-4-oxopiperidine-3-carboxylate hydrochloride (**1b**·HCl; 500 mg, 0.17 mmol) was dissolved in tap water (10 ml) and added to a suspension of commercial (*COOP*, Zurich) lyophilized bakers' yeast (50 g) in tap water (500 ml) at  $28^{\circ}$  and the mixture gently shaken for 60 h. After centrifugation (5000 rpm, 10 min), the supernatant was continuously extracted with  $\text{Et}_2\text{O}$ , and dried after evaporation ( $50^{\circ}/0.05$  Torr) to yield the crude product as a brownish oil (190 mg, 45%). Anal. HPLC (*Chiralcel*<sup>®</sup> OD-H, hexane/*sec*-BuOH 60:1): (+)-**10** ( $k' = 9.1$ , de 97%, ee > 99%) and ( $\pm$ )-**11** ( $k' = 12.7$  and  $13.8$ , de 3%, ee ca. 0%). CC ( $\text{SiO}_2$ ,  $\text{AcOEt}$ ) afforded from the main fraction pure (+)-**10** (182 mg).

Data of (+)-**10**.  $[\alpha]_D = +33.7$  (ee > 99%). All other data identical with those of ( $\pm$ )-**10**.

5. (R)- and (S)-MTPA Esters for the Tentative Determination of the Absolute Configuration of (+)-**10**. Following *Exper. 3*, a mixture of 4-hydroxy ester (+)-**10** (20 mg, 0.08 mmol) in abs.  $\text{CH}_2\text{Cl}_2$  (2 ml),  $\text{Et}_3\text{N}$  (25  $\mu\text{l}$ ), and DMAP (2 mg) was treated with (+)-(*S*)- or (–)-(*R*)-MTPA–Cl (18  $\mu\text{l}$ , 1.2 equiv.) at r.t. for 4 h. Workup and CC ( $\text{SiO}_2$ ,  $\text{Et}_2\text{O}$ ) of the crude products afforded the MTPA esters **12a** (26.2 mg, 70%) and **12b** (28.3 mg, 76%), both as colorless, viscous oils.

Data of the (R)- and (S)-MTPA Esters of (+)-**10**. Methyl (3*R*,4*S*)-1-Benzyl-4-[ (2*R*)-3,3,3-trifluoro-2-methoxy-1-oxo-2-phenylpropoxy]piperidine-3-carboxylate ((*R*)-MTPA ester **12a**).  $R_f$  ( $\text{Et}_2\text{O}$ ) 0.61.  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ ): 7.42–7.20 (m,  $\text{PhCH}_2$ , Ph); 5.61 (s,  $w_{1/2} \approx 10$ , H–C(4)); 3.84, 3.78 (AB,  $^2J = 13.0$ ,  $\text{PhCH}_2$ ); 3.51 (s, COOMe); 3.35 (q,  $^3J(\text{Me},\text{F}) = 1.0$ , MeO); 3.32 (br. d,  $^2J = 12.5$ ,  $\text{H}_{\text{eq}}\text{--C}(2)$ ); 3.21 (m, *d*-like,  $w_{1/2} \approx 28$ , H–C(3)); 3.02 (br. d,  $^2J \approx 11$ ,  $w_{1/2} \approx 22$ ,  $\text{H}_{\text{eq}}\text{--C}(6)$ ); 2.55 (t,  $^2J \approx ^3J(2_{\text{ax}},3) = 12.5$ ,  $\text{H}_{\text{ax}}\text{--C}(2)$ ); 2.19 (t,  $^2J \approx ^3J(6_{\text{ax}},5_{\text{ax}}) \approx 11$ ,  $\text{H}_{\text{ax}}\text{--C}(6)$ ); 2.13 (br. *t*-like,  $^2J \approx 13$ ,  $^3J(5_{\text{ax}},6_{\text{ax}}) \approx 11$ ,  $\text{H}_{\text{ax}}\text{--C}(5)$ ); 1.95 (br. d,  $^2J \approx 13$ ,  $w_{1/2} \approx 20$ ,  $\text{H}_{\text{eq}}\text{--C}(5)$ ).  $^{13}\text{C-NMR}$  (125.8 MHz,  $\text{CDCl}_3$ ): 171.4 (COOMe); 169.3 (CO of MTPA); 131.9 (C(1')); 130.9 (C(1'')); 130.0 (C(2'), C(6')); 129.1 (C(3'), C(5')); 128.8 (C(2''), C(6'')); 128.2 (C(3''), C(5'')); 1227.7 (C(4')); 127.6 (C(4'')); 123.4 (q,  $^1J(\text{C},\text{F}) = 289$ ,  $\text{CF}_3$ ); 84.7 (d,  $^3J(\text{C},\text{F}) = 28$ ,  $\text{PhC}(\text{OMe})(\text{CF}_3)\text{C}(=\text{O})$ ); 69.5 (C(4)); 61.8 ( $\text{PhCH}_2$ ); 55.4 (COOMe); 52.4 (MeO); 48.1 (C(2)); 46.6 (C(6)); 43.2 (C(3)); 27.9 (C(5)).

*Methyl (3R,4S)-1-Benzyl-4-[(2S)-3,3,3-trifluoro-2-methoxy-1-oxo-2-phenylpropoxy]piperidine-3-carboxylate ((S)-MTPA ester 12b):*  $R_f$  (Et<sub>2</sub>O) 0.66. <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>): 7.45–7.15 (*m*, PhCH<sub>2</sub>, Ph); 5.61 (*s*,  $w_{1/2} \approx 10$ , H–C(4)); 3.53 (*s*, COOMe); 3.42 (*q*,  $^3J(\text{Me},\text{F}) = 1.0$ , MeO); 3.43, 3.40 (*AB*,  $^2J = 13.0$ , PhCH<sub>2</sub>); 2.96 (*br. d*,  $^2J \approx 10$ ,  $w_{1/2} \approx 22$ , H<sub>eq</sub>–C(2)); 2.82 (*m*,  $w_{1/2} \approx 28$ , H–C(3)); 2.54 (*br. d*,  $^2J \approx 10$ ,  $w_{1/2} \approx 22$ , H<sub>eq</sub>–C(6)); 2.30 (*t*,  $^2J = ^3J(2\text{ax},3) = 11.5$ , H<sub>ax</sub>–C(2)); 1.92 (*br. t*,  $^2J \approx ^3J(5\text{ax},6\text{ax}) \approx 11$ , H<sub>ax</sub>–C(5)); 1.86 (*m*, *t*-like,  $^2J \approx ^3J(6\text{ax},5\text{ax}) \approx 11$ , H<sub>ax</sub>–C(6)); 1.80 (*br. d*-like,  $^2J \approx 11$ , H<sub>eq</sub>–C(5)). <sup>13</sup>C-NMR (125.8 MHz, CDCl<sub>3</sub>): 171.1 (COOMe); 165.7 (CO of MTPA); 132.6 (C(1')); 132.3 (C(1'')); 129.8 (C(2'), C(6')); 129.2 (C(3'), C(5')); 129.0 (C(2''), C(6'')); 128.6 (C(3''), C(5'')); 128.5 (C(4'')); 127.6 (C(4'')); 123.5 (*q*,  $^1J(\text{C},\text{F}) = 289$ , CF<sub>3</sub>); 84.8 (*d*,  $^2J(\text{C},\text{F}) = 27.8$ , PhC(OMe)(CF<sub>3</sub>)C(=O)); 71.2 (C(4)); 63.1 (PhCH<sub>2</sub>); 55.6 (COOMe); 52.1 (MeO); 49.5 (C(2)); 47.4 (C(6)); 45.1 (C(3)); 29.6 (C(5)).

$\Delta\delta(\text{H}) = \delta(\text{S}) - \delta(\text{R})$  (in Hz): H–C(4), 0<sup>3</sup>; H<sub>ax</sub>–C(2), –125; H<sub>eq</sub>–C(2), –180; H–C(3), –195; H<sub>ax</sub>–C(5), –105; H<sub>eq</sub>–C(5), –75; H<sub>ax</sub>–C(6), –165; H<sub>eq</sub>–C(6), –240. The  $\Delta\delta$  values do not allow a configurational assignment.

6. *Reduction of (+)-10 to (+)-3.* The (3R,4S)-carboxylate (+)-10 (52 mg, 0.198 mmol) in abs. Et<sub>2</sub>O (2 ml) was added to LiAlH<sub>4</sub> (1.5 mg, 0.38 mmol, 2 equiv.) in abs. Et<sub>2</sub>O (2 ml) at ca. 5° over 30 min, and the suspension was stirred at r.t. (3 h). Then 2,2',2''-nitrilotris[ethanol] (60 mg) was added slowly at ca. 5°, and after 30 min, H<sub>2</sub>O (15 µl) was added and the mixture stirred for 15 h at r.t. The resulting suspension was filtered over *Celite*, thoroughly washed with Et<sub>2</sub>O, and dried at 30°/0.05 Torr. CC (SiO<sub>2</sub>, Et<sub>2</sub>O) afforded (+)-3 (40.3 mg, 92%) as colorless crystals ( $[\alpha]_D = +15.6$ ). All other data: identical with those of (+)-3 (see *Exper. 2.3*) and (±)-3 [3].

7. *X-Ray Crystal Structure Determination of 6b<sup>4</sup>*. All measurements were made on a *Nonius-KappaCCD* area-detector diffractometer [22] by using graphite-monochromated MoK<sub>α</sub> radiation ( $\lambda$  0.71073 Å) and an *Oxford-Cryosystems Cryostream-700* cooler. The unit-cell constants and an orientation matrix for data collection were obtained from a least-squares refinement of the setting angles of 5170 reflections in the range  $4^\circ < 2\theta < 55^\circ$ . The mosaicity was  $0.412(1)^\circ$ . A total of 219 frames were collected by using  $\phi$  and  $\omega$  scans with  $\kappa$  offsets, 36-s exposure time and a rotation angle of  $2.0^\circ$  per

Table. Crystallographic Data of 6b·(+)-(S)-MTPA

|                                              |                                                                |                                              |                                       |
|----------------------------------------------|----------------------------------------------------------------|----------------------------------------------|---------------------------------------|
| Crystallized from                            | i-PrOH                                                         | Scan type                                    | $\phi$ and $\omega$                   |
| Empirical formula                            | C <sub>43</sub> H <sub>42</sub> F <sub>9</sub> NO <sub>9</sub> | $2\theta_{(\text{max})}$ [°]                 | 55                                    |
| $M_r$                                        | 887.79                                                         | Total reflections measured                   | 60090                                 |
| Crystal color, habit                         | colorless, prism                                               | Symmetry-independent                         | 5162                                  |
| Crystal dimensions [mm]                      | $0.17 \times 0.28 \times 0.30$                                 | reflections                                  |                                       |
| Temperature [K]                              | 160(1)                                                         | $R_{\text{int}}$                             | 0.070                                 |
| Crystal system                               | orthorhombic                                                   | Reflections with $I > 2\sigma(I)$            | 4178                                  |
| Space group                                  | $P2_12_12_1$ (#19)                                             | Reflections used in                          | 5162                                  |
| $Z$                                          | 4                                                              | refinement                                   |                                       |
| Reflections for cell                         | 5170                                                           | Parameters refined                           | 567                                   |
| determination                                |                                                                | Final $R(F)$ ( $I > 2\sigma(I)$ )            | 0.0383                                |
| $2\theta$ range for cell                     | 4–55                                                           | reflections)                                 |                                       |
| determination [°]                            |                                                                | $wR(F^2)$ (all data)                         | 0.0919                                |
| Unit cell parameters: $a$ [Å]                | 11.0411(1)                                                     | Weights                                      | $w = [\sigma^2(F_o^2) + (0.0517P)]^2$ |
| $b$ [Å]                                      | 17.3020(3)                                                     |                                              | $+ 0.0985P]^{-1}$ ,                   |
| $c$ [Å]                                      | 21.2433(4)                                                     |                                              | where $P = (F_o^2 + 2F_c^2)/3$        |
| $\alpha$ [°]                                 | 90                                                             | Goodness of fit                              | 1.092                                 |
| $\beta$ [°]                                  | 90                                                             | Secondary extinction                         | 0.030(1)                              |
| $\gamma$ [°]                                 | 90                                                             | coefficient                                  |                                       |
| $V$ [Å <sup>3</sup> ]                        | 4058.2(1)                                                      | Final $\Delta_{\text{max}}/\sigma$           | 0.001                                 |
| $F(000)$                                     | 1840                                                           | $\Delta\rho$ (max; min) [e Å <sup>−3</sup> ] | 0.28; −0.24                           |
| $D_x$ [g cm <sup>−3</sup> ]                  | 1453                                                           | $\sigma(d_{(\text{C}-\text{C})})$ [Å]        | 0.003–0.004                           |
| $\mu(\text{MoK}_\alpha)$ [mm <sup>−1</sup> ] | 0.128                                                          |                                              |                                       |

frame, and a crystal-detector distance of 31.8 mm. Data reduction was performed with HKL Denzo and Scalepack [23]. The intensities were corrected for *Lorentz* and polarization effects, but not for absorption. The space group was uniquely determined by the systematic absences. Equivalent reflections were merged. The data collection and refinement parameters are compiled in the *Table*. The structure was solved by direct methods with SIR92 [24] which revealed the positions of all non-H-atoms. The non-H-atoms were refined anisotropically. The ammonium H-atom was placed in the position indicated by a difference-electron-density map, and its position was allowed to refine together with an isotropic displacement parameter. All remaining H-atoms were placed in geometrically calculated positions and refined by using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to  $1.2U_{eq}$  of its parent C-atom ( $1.5U_{eq}$  for the methyl groups). The refinement of the structure was carried out on  $F^2$  by using full-matrix least-squares procedures, which minimized the function  $\sum w(F_o^2 - F_c^2)^2$ . The weighting scheme was based on counting statistics and included a factor to downweight the intense reflections. Plots of  $\sum w(F_o^2 - F_c^2)^2$  vs.  $F_o/F_c(\max)$  and resolution showed no unusual trends. A correction for secondary extinction was applied. Neutral-atom scattering factors for non-H-atoms were taken from [25], and the scattering factors for H-atoms were taken from [26]. Anomalous dispersion effects were included in  $F_c$  [27]; the values for  $f'$  and  $f''$  were those of [28]. The values of the mass attenuation coefficients are those of [29]. The SHELXL97 program [30] was used for all calculations.

## REFERENCES

- [1] W. Ganci, E. J. M. Meier, F. Merckling, G. Przibille, U. Ringeisen, P. Rüedi, *Helv. Chim. Acta* **1997**, *80*, 421; S. Furegati, W. Ganci, G. Przibille, P. Rüedi, *Helv. Chim. Acta* **1998**, *81*, 1127; S. Furegati, O. Zerbe, P. Rüedi, *Chem.-Biol. Interact.* **2005**, *157–158*, 48; M. J. Stöckli, P. Rüedi, *Helv. Chim. Acta* **2007**, *90*, 2058.
- [2] S. Furegati, F. Gorla, A. Linden, P. Rüedi, *Chem.-Biol. Interact.* **2005**, *157–158*, 415.
- [3] S. Furegati, W. Ganci, F. Gorla, U. Ringeisen, P. Rüedi, *Helv. Chim. Acta* **2004**, *87*, 2629.
- [4] C. Clerc, 'Synthese und Charakterisierung von enantiomerenreinen N-heterocyclischen Phosphadecalinen als Inhibitoren von Acetylcholinesterase', Ph.D. Thesis, University of Zurich, 2008.
- [5] J. A. Dale, D. L. Dull, H. S. Mosher, *J. Org. Chem.* **1969**, *34*, 2543; G. R. Sullivan, J. A. Dale, H. S. Mosher, *J. Org. Chem.* **1973**, *38*, 2143; J. A. Dale, H. S. Mosher, *J. Am. Chem. Soc.* **1973**, *95*, 512; I. Ohtani, T. Kusumi, Y. Kahman, H. Kakisawa, *J. Am. Chem. Soc.* **1991**, *113*, 4092.
- [6] P. A. Lorenzetto, A. Strehler, P. Rüedi, *Helv. Chim. Acta* **2006**, *89*, 3023.
- [7] D. Seebach, S. Roggo, T. Maetzke, H. Braunschweiler, J. Cercus, M. Krieger, *Helv. Chim. Acta* **1987**, *70*, 1605.
- [8] I. Matarazzo, 'Der stereochemische Verlauf der Reduktion von 4-Oxopiperidin-3-carboxylaten mit Bäckerhefe', M.Sc. Thesis, University of Zurich, 2008.
- [9] D. Seebach, S. Roggo, J. Zimmermann, 'Stereochemistry of Organic and Bioorganic Transformations', Workshop Conferences, Hoechst, Vol. 17, Eds. W. Bartmann and K. B. Sharpless, VCH-Verlagsgesellschaft Weinheim, 1987.
- [10] C. J. Shi, B. Zhou, A. S. Gopalan, W. R. Shieh, F. Van Middlesworth, in 'Selectivity – a Goal for Synthetic Efficiency', Workshop Conferences, Hoechst, Vol. 14, Eds. W. Bartmann and B. M. Trost, Verlag Chemie, Weinheim, 1983; J. C. Shi, C.-S. Chen, *Angew. Chem.* **1984**, *96*, 556; R. Csuk, B. Glänzer, *Chem. Rev.* **1991**, *91*, 49.
- [11] C.-H. Wong, G. Whitesides, 'Enzymes in Synthetic Organic Chemistry', Pergamon, Oxford, 1995, p. 139.
- [12] H. Ripperger, K. Schreiber, *Ber. Dtsch. Chem. Ges.* **1969**, *102*, 2864.
- [13] G. Bettoni, E. Duranti, V. Tortorella, *Gazz. Chim. Ital.* **1972**, *102*, 189.
- [14] D. W. Knight, N. Lewis, A. C. Share, D. Haigh, *Tetrahedron: Asymmetry* **1993**, *4*, 625; D. W. Knight, N. Lewis, A. C. Share, D. Haigh, *J. Chem. Soc., Perkin Trans. 1* **1998**, 3673.
- [15] E. Brygesen, J. Nielsen, M. Willert, M. Bols, *Tetrahedron Lett.* **1997**, *32*, 5697; M. Willert, M. Bols, *Acta Chem. Scand.* **1998**, *52*, 461.

- [16] X. Liang, A. Lohse, M. Bols, *J. Org. Chem.* **2000**, 65, 7432.
- [17] M. Roberti, R. Rondanin, R. Ferroni, R. Barucchello, F. P. Invidiata, V. Andrisano, C. Bertucci, V. Bertolasi, S. Grimaudo, M. Tolomeo, D. Simoni, *Tetrahedron: Asymmetry* **2000**, 11, 4397.
- [18] M. Solymár, E. Forró, F. Fülöp, *Tetrahedron: Asymmetry* **2004**, 15, 3281.
- [19] R. W. Hoffman, *Chem. Rev.* **1989**, 89, 1841.
- [20] A. Jourdan, J. Zhu, *Tetrahedron Lett.* **2000**, 41, 7033.
- [21] M. Wächter, P. Rüedi, in preparation.
- [22] R. Hooft, KappaCCD Collect Software, Nonius BV, Delft, The Netherlands, 1999.
- [23] Z. Otwinowski, W. Minor, in 'Methods in Enzymology', Vol. 276, 'Macromolecular Crystallography', Part A, Eds. C. W. Carter Jr., and R. M. Sweet, Academic Press, New York, 1997, pp. 307–326.
- [24] A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, *J. Appl. Crystallogr.* **1994**, 27, 435.
- [25] E. N. Maslen, A. G. Fox, M. A. O'Keefe, in 'International Tables for Crystallography', Ed. A. J. C. Wilson, Kluwer Academic Publishers, Dordrecht, 1992, Vol. C, Table 6.1.1.1, pp. 477–486.
- [26] R. F. Stewart, E. R. Davidson, W. T. Simpson, *J. Chem. Phys.* **1965**, 42, 3175.
- [27] J. A. Ibers, W. C. Hamilton, *Acta Crystallogr.* **1964**, 17, 781.
- [28] D. C. Creagh, W. J. McAuley, in 'International Tables for Crystallography', Ed. A. J. C. Wilson, Kluwer Academic Publishers, Dordrecht, 1992, Vol. C, Table 4.2.6.8, pp. 219–222.
- [29] D. C. Creagh, J. H. Hubbell, in 'International Tables for Crystallography', Ed. A. J. C. Wilson, Kluwer Academic Publishers, Dordrecht, 1992, Vol. C, Table 4.2.4.3, pp. 200–206.
- [30] G. M. Sheldrick, 'SHELXL97, Program for the Refinement of Crystal Structures', University of Göttingen, Germany, 1997.

Received July 11, 2008