Pergamon

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Tetrahedron: *Asymmetry* 14 (2003) 1541–1545

TETRAHEDRON: *ASYMMETRY*

Chemoenzymatic preparation of non-racemic *N*-Boc-piperidine-3,5-dicarboxylic acid 3-methyl esters and their 5-hydroxymethyl derivatives

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Received 11 February 2003; accepted 31 March 2003

Abstract—For the synthesis of (*R*,*R*)- and (*S*,*S*)-*N*-Boc-5-hydroxymethyl-piperidine-3-carboxylic acid methyl ester as important basic units for potential inhibitors of aspartyl proteases, the respective non-racemic 3,5-dicarboxylic acid monomethyl esters were prepared as key intermediates from a *cis*,*trans*-mixture of the respective diester by several consecutive enzymatic reactions using Lipase AY, Chirazyme L-3, Hydrolase ESP-ESL-1064 and pig liver esterase.

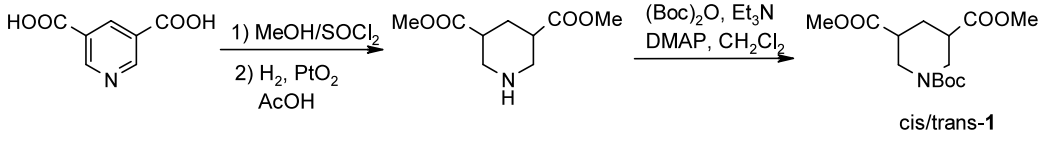
1. Introduction

3,5-Substituted piperidines are important basic units for alkaloids,[1] high affinity agonists of human GABA-A receptors,[2] farnesyl-protein transferase inhibitors[3] and continue to be fundamental moieties in pharmaceutical research.[4] In addition, it is well known that the piperidine moiety can be an efficient partner for a catalytic aspartic acid residue and therefore could be used as a central template for aspartic acid protease inhibitors.[5]

For the synthesis of the chiral key intermediates **2a** or **2b** we envisaged the *enzymatic* transformation of a *cis*/*trans* mixture of dimethyl ester **1** as the primary substrate. Beside the successful enzymatic racemic resolutions of a number of piperidine monocarboxyl ester compounds also the stereoselective monohydrolyses of *cis*-configurated piperidine-3,5-mesodiesters, namely dimethyl *N*-benzyl-*cis*-piperidine-3,5-dicarboxylate[6] and dimethyl *N*-Boc-all-*cis*-4-hydroxy-piperidine-3,5-dicarboxylate,[7] have been described. However, to the best of our knowledge, the enantioselective hydrolysis of *trans*-configured piperidine-3,5-dicarboxylic acid diesters has remained unexplored to date. Herein we describe the enzymatic preparation of both the (*S*,*S*)- and (*R*,*R*)-enantiomers of *N*-Boc-piperidine-3,5-dicarboxylic acid monomethyl ester **2a** and **2b** from the *cis*,*trans*-mixture of the respective diester **1** by several consecutive enzymatic reactions (Scheme 2).

2. Results and discussion

The preparation of the *cis*,*trans*-diester substrate **1** was carried out according to Curran et al.[8] from the 3,5-pyridinedicarboxylic acid via esterification and hydrogenation of the pyridine ring followed by protection with Boc anhydride (Scheme 1). A fivefold enrichment of the *trans*-isomer was achieved by partial crystallization of the *cis*-isomer from hexane.



Scheme 1. Synthesis of the *cis*/*trans*-diester substrate **1** from 3,5-dicarboxypyridine.

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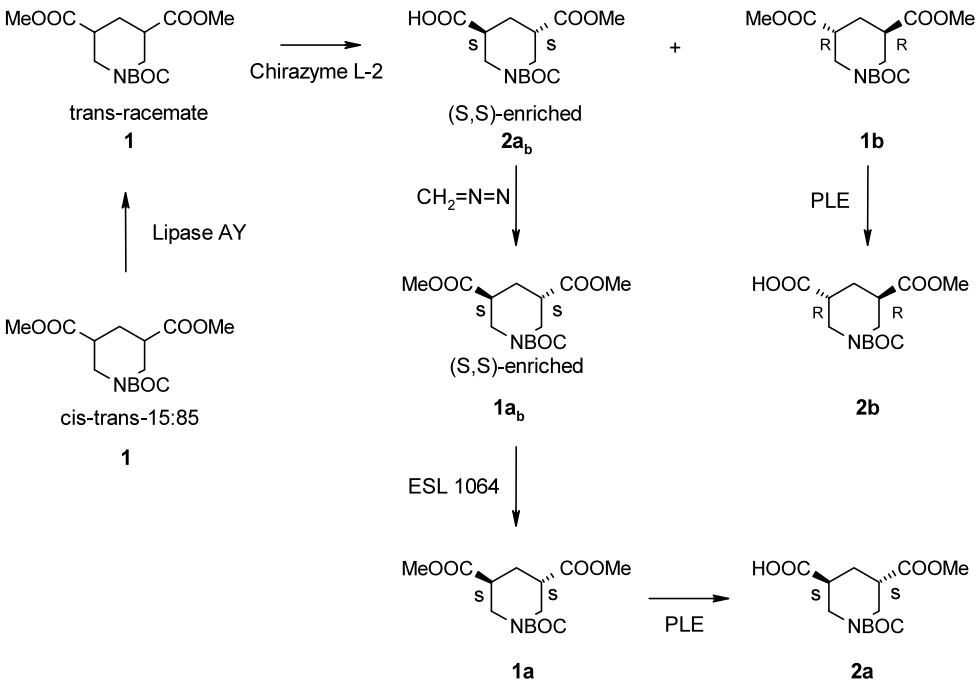
0957-4166/03/$ - see front matter
doi:10.1016/S0957-4166(03)00283-0



Scheme 2. Preparation of both monomethyl ester enantiomers **2a** and **2b** from racemic *cis*,*trans*-dimethyl ester **1** by several consecutive enzymatic reactions.

The sequence of enzymatic resolution steps started with the separation of the 15:85 *cis*/*trans*-mixture of dimethyl ester **1** by selective hydrolysis of the *cis*-diester with a commercially available hydrolase. The *cis*/*trans* selectivity of hydrolases was screened in a well plate assay based on the color change of a pH indicator. Pure geometric isomers were employed as substrates. 28 out of 69 commercial esterases/lipases tested showed activity for both isomers, nine among them preferring the *cis-meso*-diester and one the *trans*-diester **1**. Re-evaluation of the *cis*-selective group in small-scale experiments provided three enzymes with reasonable *cis*/*trans*-selectivity (Lipase AY, Chirazyme L-3 (both from *Candida rugosa*) and Lipase S2B from *Rhizopus japonicus*). Of these, Lipase AY displayed both a high selectivity (*trans*/*cis*) and activity and was selected for the preparative scale. A 12 g-experiment afforded essentially pure *trans*-isomer **1** (0.2% *cis*) in 84% yield.

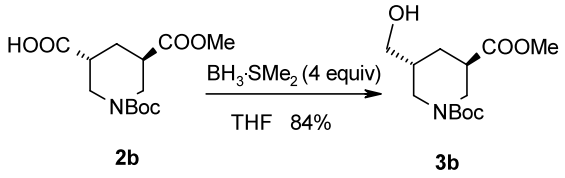
For the subsequent resolution of racemic *trans*-diester **1** all 28 active enzymes were re-evaluated on an automated pH-stat affording one reasonably selective enzyme, Chirazyme L-2 (*Candida antarctica* lipase, form *B*) preferentially hydrolyzing the (*S*,*S*)-enantiomer with an *E*-value[9] of ~39. Because of the lack of absolute enantioselectivity (*E*>200) an extended enzyme screening was carried out leading to Hydrolase ESP-ESL-1064 (Diversa Corporation) with preference for the opposite enantiomer (*E*~32). With these two moderately selective enzymes of opposite selectivity in hand we could pursue our fall-back strategy of generating first each of the two antipodes in high enantiomeric excess as the *retained* diesters **1a** and **1b** followed by monohydrolysis to the respective monoacids **2a** and **2b**. It is well known that with a moderate enzyme selectivity the *retained* enantiomer can be prepared more efficiently in high enantiomeric excess combined with a good chemical yield (cf. Sih et al.[9]) than the formed enantiomer. For a clean monohydrolysis of the diesters **1a** and **1b** pig liver esterase (PLE), which is well-known for not being able to accept negatively charged substrates, was the catalyst of choice.

(*R*,*R*)-Diester **1b** of high enantiomeric purity (>99%) was prepared by hydrolyzing *trans*-diester **1** with Chirazyme L-2. The resulting (*S*,*S*)-enriched monoester $\mathbf{2a}_b$ was re-esterified with diazomethane. The recovered (*S*,*S*)-enriched diester $\mathbf{1a}_b$ was submitted to the second resolution step catalyzed by hydrolase ESP-ESL-1064 with preference for the minor component **1b** providing the retained (*S*,*S*)-diester **1a** in high enantiomeric excess (>97%). The diesters **1a** and **1b** were monohydrolyzed smoothly with PLE to the respective monoesters **2a** and **2b**. The overall yield (with respect to the *trans*-isomer) for the whole enzymatic sequence on the g-scale was 46.7% for **2a** and 61.3% for **2b**.

Workup was not straightforward because the mono- and diester products were not properly separated after three extraction steps (observed with several organic solvents). Therefore, both the aqueous and the organic phase had to be subjected to an additional washing step.

The absolute configuration of the reaction products was established by the formation of a diastereoisomeric salt of the (*S*,*S*)-monoacid **2a** with the (S)-phenylethylamine and its subsequent crystallization and X-ray analysis.

The non-racemic hydroxymethyl esters **3a** and **3b** were obtained by selective reduction of the carboxy group in **2a** and **2b**, respectively, using 4 equiv. of the borane dimethylsulfide complex (Scheme 3).



2b **3b**

Scheme 3. Selective reduction of monoacid **2b** by means of a borane dimethylsulfide complex.

3. Conclusion

By a linear sequence of four and three enzymatic steps, respectively, the methyl *N*-Boc-piperidine-3,5-dicarboxylates (*S*,*S*)-**2a** and (*R*,*R*)-**2b** could be prepared from the corresponding *cis*/*trans*-diester **1** in high enantiomeric excesses (>96%) and good overall yield of 23% and 31%, respectively (with respect to *trans*). Selective reduction of the non-racemic monoacids **2a** and **2b** leads to the corresponding hydroxymethyl esters **3a** and **3b** which upon further derivatization allow access to several series of interesting non-racemic compounds.

4. Experimental

4.1. General

NMR-spectra: Bruker DPX 400 MHz. IR-spectra: Nicolet, FT-IR 20 SXB. EI-MS-spectra: SSQ7000 (Finnigan MAT). ISN- and ISP-MS-spectra: API 365 Triple-Quadrupol (PE SCIEX). Optical rotations: Perkin–Elmer Polarimeter 241.

4.2. Materials

Hydrolase ESP-ESL-1064 was purchased from Diversa Corporation (San Diego), Chirazyme L-2 (ex *C. antarctica*, form B) from Roche Diagnostics, Lipase AY (ex *C. rugosa*) from Amano Pharmaceuticals Co. (Nagoya) and PLE (suspension, Fluka No. 46063) from Fluka (Buchs). Diazomethane and diazoethane solutions (in ether; concentration not determined) were prepared by our kilolab service according to standard procedures. Dimethyl *cis*/*trans*-piperidine-3,5-dicarboxylate was synthesized according to Curran et al.[8] and used without further purification. The filter aid Dicalite was from Acros, all other reagents were from Fluka or Merck.

4.2.1. (1:1)- and (1:5)-Dimethyl *cis*/*trans*-*N*-Boc-piperidine-3,5-dicarboxylate 1. 51.9 g (258 mmol) of a 1:1 *cis*/*trans*-mixture of dimethyl piperidine-3,5-dicarboxylate was dissolved in 590 ml of methylene chloride under argon, and 53.9 ml (387 mmol) triethylamine was added followed by 56.3 g (258mmol) di-*tert*-butyl dicarbonate and 6.0 g (51.6 mmol) 4-(dimethylamino)pyridine. The solution was stirred at room temperature overnight. The reaction was quenched by addition of a saturated 300 ml of NH_4Cl solution followed by extraction with methylene chloride. The combined organic phases were concentrated and washed with a 0.5 M solution of $KHSO_4$. The organic phase was dried with $MgSO_4$ and concentrated to give a 1:1 mixture (64 g, 82%) of the *cis*/*trans*-diester **1**. ^{1}H NMR (400 MHz; $CDCl_3$): 1.45 (s, 9H, Boc from *trans*), 1.46 (s, 9H, Boc from *cis*), 1.69 (d.d. 1H, -CH- from *cis*), 2.08 (bm, 2H, -CH_2- from *trans*), 2.40–2.52 (m, 3H, -CH-, -$CHCO_2$- from *cis*), 2.68–2.71 (m, 2H, -NCH- from *cis*), 2.78–2.85 (m, 2H, -$CHCO_2$ from *trans*) 3.4–3.9 (bm, 4H, -NCH_2- from *trans*) interferred by 3.70 (s, 12H, CO_2CH_3 from *cis* and *trans*), 4.36 (bm, 2H, -NCH- from *cis*). EI MS: 244.4 (*M*–^{t}Bu), 242.2 (*M*–$COOCH_3$), 228.1 (*M*–^{t}BuO), 200.1 (*M*–CO_2^tBu). IR (neat): 1732 (ester), 1690 (carbamate), 1366 (*t*-butyl), 1196 (ester). In approx. 500 ml of hexane part of the *cis*-compound precipitated as a white solid that was filtered off. The filtrate was concentrated to give a ~1:5-mixture of the *cis*/*trans*-diester as a light yellow oil.

4.2.2. pH-indicator assay. Into 96 well plates pre-loaded with 0.5 mg enzyme/well a buffered pH-indicator solution (190 μl, 7.5 mM Tris–HCl, pH 8.0, 0.02% NaN_3, 50 mg/l cresol red) and the substrate solution (0.5 mg **1** in 10 μl MeOH) were added with a liquid handler (Lissy; Zinsser Analytics). The color change of the indicator from red to yellow was monitored for up to 2 days at 410 nm with a well plate reader (Tecan Sunrise) and a well plate autosampler (Twister).

4.2.3. Automated pH-stat screening procedure. 25–30 mg (82.5–99.6 μmol) diester was placed as a MeOH solution (0.3 ml) into a reactor (Metrohm pH-stat). After addition of the reaction buffer (16 ml 0.1 M NaCl, 3 mM potassium phosphate buffer pH 5.6, 0.02% NaN_3) and adjustment of the pH to 7.5 the reaction was started by adding an enzyme aliquot as buffer solution (~3–10 mg lyophilisate in 3.5 ml reaction buffer). The pH was kept constant at 7.5 under vigorous stirring by the controlled addition of 0.05N NaOH solution. After termination of the reaction (~10–50% conversion; maximal 3–5 h) the reaction mixture was acidified to pH 2.5 with 0.5N HCl and extracted with 10–20 ml CH_2Cl_2. The organic phase was subjected to GLC analysis for ee-determination of the reaction products.

4.2.4. Dimethyl *trans*-*N*-Boc-piperidine-3,5-dicarboxylate 1. 12.5 g (41.48 mmol) *cis*/*trans*-diester (85.1%, 35.30 mmol *trans*) was dissolved in 170 ml cyclohexane and the solution emulsified under vigorous stirring in 840 ml 0.1 M NaCl, 3 mM potassium phosphate buffer pH 7.5. 420 mg of Lipase AY was added and the pH kept constant by the controlled addition (pH-stat) of 1.0N NaOH solution. After consumption of 12.58 ml (30% conversion; 25 h) the reaction mixture was extracted twice with 750 ml EtOAc and the combined organic phases washed twice with 500 ml 0.1 M potassium phosphate buffer pH 7.5, dried over Na_2SO_4, evaporated and dried on a HV to give 8.95 g (84.1%

with respect to *trans*) of the *trans*-diester **1** as a yellowish oil. *Analysis:* purity: 96.0% GLC (0.2% *cis*). ^{1}H NMR (400MHz; $CDCl_3$): 1.45 (s, 9H, Boc), 2.08 (bm, 2H, -CH_2-), 2.82 (m, 2H, -$CHCO_2$-), 3.4–3.9 (bm, 4H, -NCH_2-) interferred by 3.70 (s, 6H, $COOCH_3$). ISP-MS: 302.3 (M+H^+). IR (neat): 1725 (ester), 1690 (carbamate), 1387 (*t*-butyl), 1195 (ester).

4.2.5. Dimethyl (*R*,*R*)-*N*-Boc-piperidine-3,5-dicarboxylate 1b. 8.95 g (96%; 28.51 mmol) *rac*,*trans*-diester **1** was dissolved in 100 ml TBME and emulsified under vigorous stirring in 900 ml 0.1 M NaCl, 20 mM potassium phosphate buffer pH 7.0. 3.3 g of Chirazyme L-2 was added and the pH kept constant by the controlled addition (pH-stat) of 1.0N NaOH solution. After the retained enantiomer **1b** had reached >99% ee the reaction mixture was extracted thrice with 1 l CH_2Cl_2 (for better phase separation the emulsions were filtered through 50 g Dicalite each time, the combined filter cakes re-extracted with EtOAc and the extract combined with the organic phases). The combined organic phases were washed with 500 ml of 0.1 M phosphate buffer pH 8.0, dried over Na_2SO_4, evaporated and dried on a HV to give 3.69 g (41.2%) of the chiral diester **1b**. *Analysis:* purity: 97.7% GLC (ethylated); >99% ee. Specific rotation $[\alpha]_D$ −47.7 [*c* 1.1; $CHCl_3$].

4.2.6. (*S*,*S*)-Enriched dimethyl *N*-Boc-piperidine-3,5-dicarboxylate 1a$_b$. The aqueous phase of the above experiment was set to pH 2.5 with 25% hydrochloric acid and extracted with 3×1 l EtOAc. The combined organic phases were dried over Na_2SO_4, evaporated and dried on a HV to give 4.05 g (47.5%; 97.9% GLC) of (*S*,*S*)-enriched monoester **2a**$_b$. The yellowish oil was dissolved in 10 ml of dry Et_2O and a total of 300 ml freshly prepared diazomethane solution (Et_2O) added in portions under vigorous stirring (development of N_2). The solution was stirred overnight, washed with 250 ml of 0.1 M phosphate buffer pH 8.0, dried over Na_2SO_4, evaporated and dried on a HV to give 3.70 g (87.1%; 98.7% GLC; 79%ee) of a yellow oil.

4.2.7. Dimethyl (*S*,*S*)-*N*-Boc-piperidine-3,5-dicarboxylate 1a. 3.70 g (98.7%; 12.12 mmol) (*S*,*S*)-enriched diester **1a**$_b$ was dissolved in 5 ml MeOH and emulsified under vigorous stirring in 800 ml 0.1 M NaCl, 3 mM potassium phosphate buffer pH 7.5. 70 mg of lyophilized enzyme ESL 1064 was added and the pH kept constant by the controlled addition (pH-stat) of 1.0N NaOH solution. After consumption of 5.37 ml (44% conversion; 10 days) the reaction mixture was extracted thrice with 500 ml CH_2Cl_2. The combined organic phases were washed with 250 ml of 0.1 M phosphate buffer pH 7.5, dried over Na_2SO_4, evaporated and dried on a HV to give 2.40 g (64.9%) of the chiral diester **1a**. *Analysis:* purity: 93.4% GLC (ethylated); 97.7% ee. Specific rotation $[\alpha]_D$ +51.8 [*c* 1.2; $CHCl_3$].

4.2.8. Methyl (*R*,*R*)-*N*-Boc-piperidine-3,5-dicarboxylate 2b. 3.69 g (97.7%;11.96 mmol) chiral diester **1b** was dissolved in 5 ml MeOH and emulsified under vigorous stirring in 750 ml 0.1 M NaCl, 3 mM potassium phosphate buffer pH 7.5. 1 ml of PLE-suspension was added and the pH kept constant by the controlled addition (pH-stat) of 1.0N NaOH solution. After consumption of 10.8 ml (termination after 90% conversion; 2 days) the reaction mixture was washed twice with 500 ml CH_2Cl_2. The aqueous phase was acidified to pH 2.5 with 25% hydrochloric acid and extracted thrice with 500 ml EtOAc. The combined organic phases were dried over Na_2SO_4, twice evaporated (redissolved in CH_2Cl_2) and dried on a HV to give 3.11 g (88.4%) of the chiral monoacid **2b**. *Analysis:* purity: 95.8% GLC (ethylated); 3% CH_2Cl_2 even after prolonged HV; >99% ee. Specific rotation $[\alpha]_D$ −48.8 [*c* 1.2; $CHCl_3$]. ^{1}H NMR (400 MHz; $CDCl_3$): 1.44 (s, 9H, Boc), 2.10 (bm, 2H, -CH_2-), 2.77–2.90 (m, 2H, -$CHCO_2$-), 3.4–3.9 (bm, 4H, -NCH_2-) interferred by 3.70 (s, 3H, $COOCH_3$), 10.3 (bs, ∼1H, COOH). ISN-MS: 286.1 (M–H^+). IR (neat): 2978 (acid), 1735 (ester), 1701 (acid), ∼1680 (carbamate), 1368 (*t*-butyl), 1297 and 1168 (ester, acid).

4.2.9. Methyl (*S*,*S*)-*N*-Boc-piperidine-3,5-dicarboxylate 2a. 2.38 g (93.4%; 7.38 mmol) (*S*,*S*)-diester **1a** was dissolved in 3 ml MeOH and emulsified under vigorous stirring in 500 ml 0.1 M NaCl, 3 mM potassium phosphate buffer pH 7.5. 0.5 ml of PLE-suspension was added and the pH kept constant by the controlled addition (pH-stat) of 1.0N NaOH solution. After consumption of 7.70 ml (1.04 equiv.; 44 h) the reaction mixture was washed twice with 500 ml CH_2Cl_2. The aqueous phase was acidified to pH 2.5 with 25% hydrochloric acid and extracted thrice with 500 ml EtOAc. The combined organic phases were dried over Na_2SO_4, evaporated and dried on a HV to give 2.37 g (104%) of the chiral monoacid **2a** as a yellowish oil. *Analysis:* purity: 93.4% GLC (ethylated); 3% of EtOAc even after prolonged HV; 96.6% ee. Specific rotation $[\alpha]_D$ +45.4 [*c* 1.26; $CHCl_3$].

4.2.10. Absolute configuration of (*S*,*S*)-monoacid 2a. To a solution of 300 mg (92.3%, 0.94 mmol) of monoacid **2a** in 5 ml CH_2Cl_2 135 μl (1.04 mmol) of (*S*)-phenethylamine was added and the mixture shaken overnight. The formed precipitate was filtered off and recrystallized from water. Fine small crystals were obtained and analyzed by X-ray. *Analysis:* ^{1}H NMR (400 MHz; $CDCl_3$): 1.42 (s, 9H, Boc), 1.50 (d, 3H, CH-CH_3), 1.97 (bm, 2H, -CH_2-), 2.61 (bm, 1H, -CH-), 2.83 (bm, 1H, -$CHCO_2$-), 3.45–3.65 (bm, 4H, -NCH_2-), 3.68 (s, 3H, $COOCH_3$), 4.23 (q, 1H, CH-CH_3), 6.52 (bm, 3H, NH_3^+), 7.33 (m, 5H, arom.). Crystallographic data indicated (*S*,*S*)-configuration and have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 190301. The unit cell parameters are *a* 12.760(3), *b* 6.3410(13), *c* 13.685(3), and *β* 96.75(3). The space group is *P*21.

4.2.11. Methyl (*R*,*R*)-*N*-Boc-5-hydroxymethyl-piperidine-3-carboxylate 3b. 734 mg (2.55 mmol) **2b** was dissolved in 10 ml anhydrous THF, and 5.1 ml (10.21 mmol) borane dimethyl sulfide (2 M in THF) is added at −20°C. The reaction was stirred for 4 h; over this period of time the temperature increased from −20°C to room temperature. 5 ml of MeOH was added and the

mixture stirred for 10 min. MeOH was removed by evaporation, 10 ml saturated solution of NH_4Cl was added and the mixture extracted thrice with 15 ml CH_2Cl_2. Drying and concentration of the organic phase gave 590 mg (84%) of a colorless oil. *Analysis:* purity: 100% GLC; >99% ee. Specific rotation $[\alpha]_D$ −41.31 [*c* 1.05; CH_2Cl_2]. ^1H NMR (400 MHz; $CDCl_3$): 1.46 (s, 9H, Boc), 1.76–1.8 (m, 1H, -CH_2-), 1.88–1.92 (m, 1H, -CH_2-), 2.01 (bm, 1H, -CH-), 2.59 (bm, 2H, NCH_2-), 3.2 (m, 1H, OH-), 3.32–3.38 (m, 1H, CHOH), 3.52 (m, 2H, NCH_2-), 3.69 (s, 4H, CO_2CH_3, CH-), 3.83–3.88 (m, 1H, CHOH). ISN-MS: 274.3 ($M-H^+$). IR (neat): 1734 (ester), 1698 (acid), 1667 (carbamate), 1366 (*t*-butyl), 1296 and 1152 (ester, acid), 1030 (alcohol).

4.2.12. Methyl (*S*,*S*)-*N*-Boc-5-hydroxymethyl-piperidine-3-carboxylate 3a. Conversion of 530 mg of monoacid **2a** under identical conditions as above gave 400 mg (79%) of **3a** as a colorless oil. *Analysis:* purity: 100% GLC; >92% ee. Specific rotation $[\alpha]_D$ +42.9 [*c* 1.0; CH_2Cl_2].

4.2.13. Enantiomeric excess. The enantiomeric excess of **1** and **2** was determined by means of GLC on a BGB-172 column (from BGB-Analytik AG, Anwil, Switzerland; 30 m×0.25 mm; H_2; 100 kPa): 130–230°C with 2°C/min; Inj.: 210°C. FID: 230°C. Retention times (min): 33.1 (*R*,*R*)-*trans*-dimethyl ester **1b**, 33.6 (*S*,*S*)-*trans*-dimethyl ester **1a**, 34.4 *cis*-dimethyl ester, 34.9 (*R*,*R*)-*trans*-methyl ester **2b** (ethylated), 35.3 (*S*,*S*)-*trans*-methyl ester **2a** (ethylated). Ethylation in diazoethane solution.

The enantiomeric excess of **3** was determined by means of GLC on a BGB-175 column (15 m×0.25 mm; H_2; 60 kPa): 100–200°C with 2°C/min; Inj.: 200°C. FID: 200°C. Retention times (min): 38.75 (*S*,*S*)-hydroxymethyl ester **3a** and 39.10 (*R*,*R*)-hydroxymethyl ester **3b**.

Acknowledgements

We express our thanks to Patrik Stocker and Peter Weiss for their skillful technical assistance and to our colleagues from the service labs for analyzing numerous samples, especially to Sabine Ulrike Mayer for the determination of the enantiomeric excess of our products and André Alker for establishing the X-ray structure.

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