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Asymmetric Synthesis of Trans-2,5-dimethylpyrrolidine

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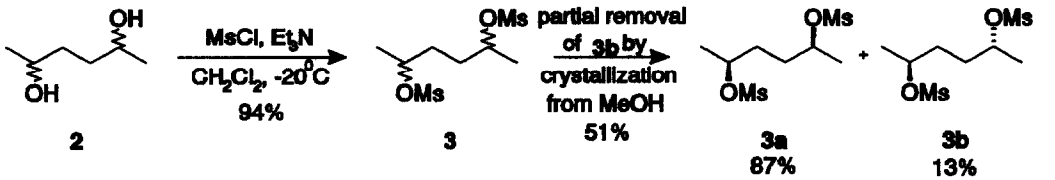
Abstract: A new synthetic route to (2S,5S)-dimethylpyrrolidine 1, which can also be applied to the synthesis of the (2R,5R)-enantiomer, has been developed. The C_2-symmetric pyrrolidine can be obtained enantiomerically pure (e.e. ≥ 97%) in 15% overall yield starting from a mixture of isomers of 2,5-hexanediol, via a short reaction sequence using (S)-α-methylbenzylamine as a chiral auxiliary. The crystal and molecular structure of (S)-2'-phenyl-N-ethyl-(2S,5S)-dimethylpyrrolidine picrate 5, showing an antiparallel stacking of the picrate units, is also reported.

The presence of a C_2-axis within a chiral auxiliary has proved to be of great importance in numerous asymmetric syntheses.[1] This success is due to a drastic reduction of competing diastereomeric transition states. One of these C_2-symmetrical chiral auxiliaries, that has already shown its synthetic value, is trans-2,5-dimethylpyrrolidine 1.[2] High selectivities have been obtained in the enantioselective alkylation of cyclohexanone using 1 as a chiral auxiliary.[2a,b] More recently stereoselective intermolecular radical additions to alkenes substituted with 1[3] and [2+2]-[4] and [4+2]-cycloadditions[5] with excellent selectivities have been reported. In the past pyrrolidine 1 could only be obtained homochiral by resolution of the racemate,[2a] but in 1987 Schlessinger and Iwanowics reported the first enantioselective synthesis of 1 starting from D- or L-alanine.[6] Recently this procedure was optimized by Welch and coworkers.[7] An alternative enantioselective synthesis was published by Short, Kennedy and Masamune,[8] starting with an enzymatic reduction of 2,5-hexanedione using Baker's yeast to yield (2S,5S)-hexanediol (e.e. > 98%). This diol was used in a three step reaction sequence to provide 1. This procedure only gives access to (2R,5R)-1. An enantioselective route to either (2S,5S)- or (2R,5R)-hexanediol, and in principle to both enantiomers of 1, was described by Burk and coworkers.[9] Our attempts to achieve a kinetic resolution of 5-alkoxy-2(5H)-furanones by means of 1,4-additions of chiral C_2-symmetric pyrrolidines urged us to develop a short route to 1. We now report a new synthetic pathway to optically pure 1.

Synthesis of (2S,5S)-dimethylpyrrolidine 1

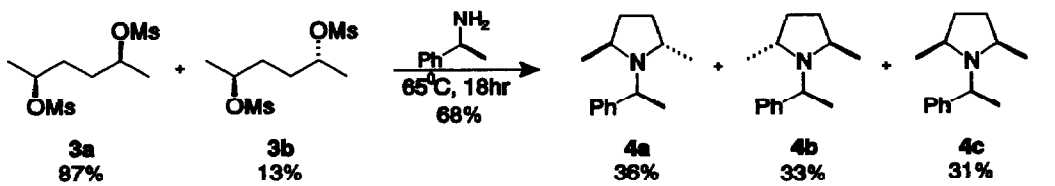
The reaction sequence we developed is partly related to the method of Masamune and coworkers,[8] but has been modified in some crucial steps. During this project we found that a similar strategy was developed independently by Yamamoto and coworkers[10] in the synthesis of optically pure 2,5-dimethoxymethylpyrrolidine.

We choose 2,5-hexanediol, as a mixture of meso- and d,l-isomers, as the readily available starting material. In our procedure the three isomers present, i.e. RR, SS and RS (meso), have to be separated at some stage during the reaction sequence.



Scheme 1

In the first step 2,5-hexanediol is converted to 2,5-hexanediol dimethanesulfonate **3** (Scheme 1). The major part of the meso isomer **3b** is removed at this stage by crystallization from methanol. After this separation step a ratio **3a:3b** of 87:13 was obtained. A complete separation of meso- and d,l-2,5-hexanediol dimethanesulfonate **3** has been claimed,[11] but the analysis was solely based on melting points. Reproduction of the reported procedure did not result in complete separation as was determined with ^{13}C-NMR. Analysis based on melting points proved to be unreliable. Also in several attempts to separate the corresponding 2,5-hexanediol di-p-toluenesulfonates in the meso- and d,l-isomers, we were not able to reproduce the results reported.[12] In our reaction sequence the route as presented in scheme 1 was used because higher yields were obtained with dimethanesulfonate **3** compared to the corresponding di-p-toluenesulfonate.

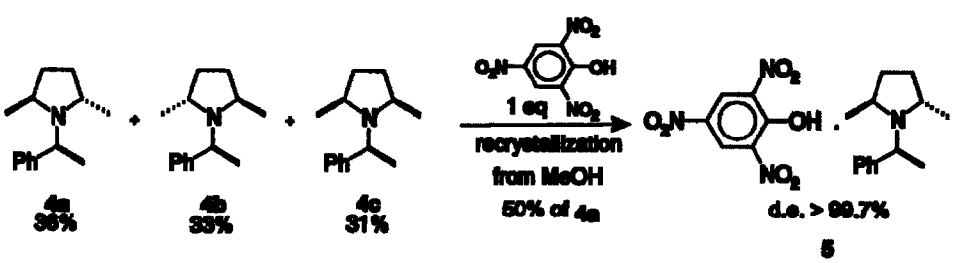


Scheme 2

The substitution-cyclization of **3a/3b** with (S)-α-methylbenzylamine yields a diastereomeric mixture of **4a**, **4b** and **4c** (Scheme 2). Complete separation of **3a** and **3b** in the former step has proven not to be essential, because the ring closure does not proceed with total inversion of stereochemistry at C2 and C5. Analogous ring closures with sulfur,[12] oxygen[13] or phosphorus[9] nucleophiles can be found in the literature, but the partial loss of stereochemical integrity we observed in this study has never been reported as far as we know. Also in the ring closure performed in the Masamune route,[8] which shows the largest analogy to our procedure, total inversion of configuration is claimed. The diminished stereospecificity we observed can be ascribed to a combination of higher reaction temperatures and the excess of α-methylbenzylamine, both of which are needed for our ring closure procedure.

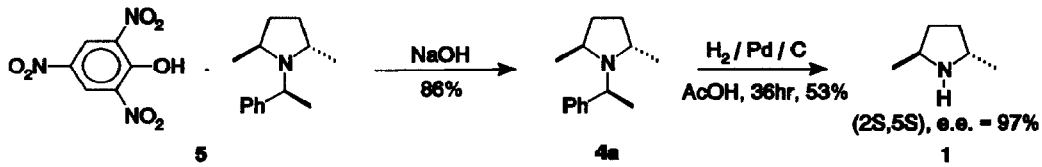
In order to obtain an optically pure product the diastereomeric mixture **4a-c** has to be separated. Firstly this separation was tried by chromatography over silica gel using ether/hexane (1 : 10) containing 1% triethylamine. Diastereomer **4a** was successfully obtained enantiomerically pure (0.25 g quantities) when the chromatographic step was executed on 1 gram scale. Only partial separation of **4a** was achieved on multigram scale. Diastereomers **4b** and **4c** could not be separated at all, not even in very small quantities. Other solvent mixtures like ethylacetate/hexane and petroleum ether/ether, did not result in the chromatographic separation of **4a-c**. Use of aluminium oxide as the column material and applying a chromatotron instead of column chromatography did not give better results. Therefore this two step procedure gives rather easy access to relative small amounts of **4a** in enantiomerically pure form but the method is not suited for larger quantities.

Next we tried to achieve a separation of the diastereoisomers **4a-c** by crystallization of the corresponding salts. Although many acids like hydrochloric acid, p-toluenesulfonic acid, some phosphoric acids and acetic acid did not give crystalline salts, good results were obtained with picric acid. Treatment of **4a-c** with 1 equivalent of picric acid in methanol resulted in a mixture of diastereomeric salts which readily crystallized from methanol. After four crystallizations from methanol **5** could be obtained diastereomerically pure (d.e. ≥ 99.7%),[14] in 50% yield (Scheme 3).



Scheme 3

All attempts to isolate **4b**, which should give access to (2R,5R)-**1**, by crystallization of the concentrated mother liquor in other solvents or via salts with other acids failed. However both enantiomers of **1** can in principle be obtained by performing the ring closure of scheme 2 with either (R)- or (S)-α-methylbenzylamine. The free amine **4a** could easily be recovered by extraction of **5**, dissolved in aqueous NaOH, with pentane. Debenzylation by reduction with hydrogen and Pd/C yielded (2S,5S)-dimethylpyrrolidine **1** ($[\alpha]_D^{20}$ -5.52 (c 1.05, CH_2Cl_2), e.e. ≥ 97%) which was in all respects identical with **1** prepared via the reported procedure[7] (Scheme 4). The e.e. of the product was determined with ^{31}P-NMR via derivatization of **1** with N,N'-bis((S)-1-phenylethyl)-1,2-ethylene-diamino-N,N'-diaza-N",N"-dimethylphospholidine.[15] The reported procedure gives readily access to (2S,5S)-**1** in gram quantities.



Scheme 4

Crystal and molecular structure determination of 5

In order to determine independently the absolute configuration of diastereomer **5**, which crystallizes preferentially, an X-ray analysis was undertaken. Yellow crystals of **5**, suitable for X-ray analysis, were obtained by crystallization from methanol by slow evaporation of the solvent. The molecular structure of **5** is presented in figure 1. Figure 1a and 1b show two chemical identical, but crystallographically independent molecules of **5**, which are present in the asymmetric unit.

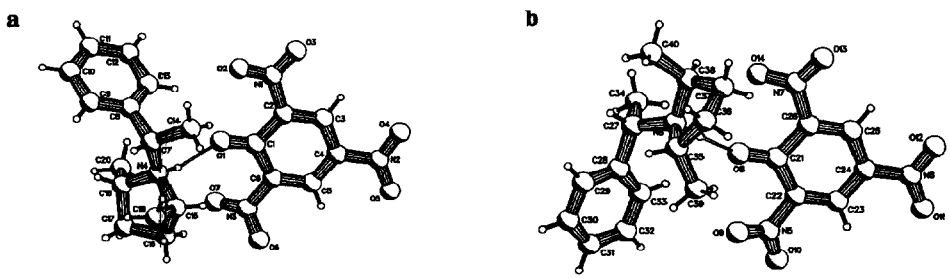


Figure 1 PLUTO plots of 5 with adopted numbering scheme

The independent molecules differ in their conformations and have different bond angles and bond lengths.[16] The ammonium hydrogen atoms were located in a difference Fourier map. The hydrogen atoms attached to N(4) and N(8) (see numbering scheme) are involved in hydrogen bonding. The assignment of the absolute configuration at C2 and C5, being (2S,5S),[17] was based on the absolute configuration of (S)-α-methylbenzylamine. No epimerization of the benzylic stereogenic center was likely to take place during the synthetic route. The crystal structure consists of molecules of an anion and cation connected by a hydrogen bond.

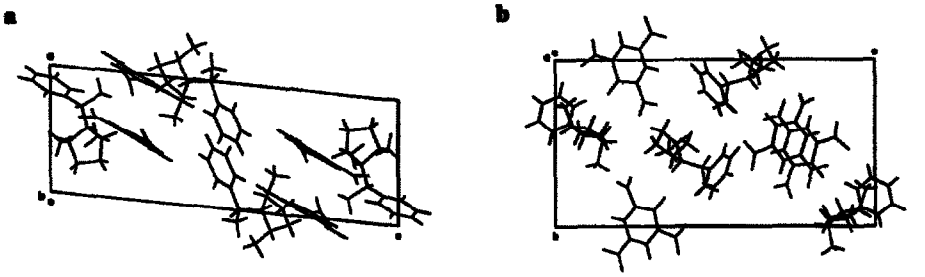


Figure 2 Crystal packing of 5

In figure 2a and 2b the packing of the molecules in the unit cell is depicted. The unit cell is viewed along the b_0- and a_0-axis respectively. In figure 2a the trinitrophenolate units are parallel to the b_0-axis and appear to stack to each other. Interactions between the trinitrophenolate- and the pyrrolidine phenyl ring are not present. These phenyl rings also do not interact with each other, as can be seen from figure 2b. It is clearly shown that the picrate units are stacked with their dipolar moments anti-parallel to each other with the phenolate oxygen atoms pointing in opposite directions. Several crystal structures of salts of amines and picric acid with different stacking patterns are known in literature.[18] A similar stacking pattern of the picrate units as the one we found, is observed in pyridinium-1-naphthylamine picrate.[18c]

Conclusions

We reported a new synthesis of (2S,5S)-dimethylpyrrolidine 1, using (S)-α-methylbenzylamine, which can also be applied to the preparation of the other enantiomer starting with (R)-α-methylbenzylamine. Compound 1 can be obtained in 15% overall yield with an e.e. ≥ 97%. The e.e. of the product is limited by the e.e. of the used α-methylbenzylamine. Unfortunately we did not achieve the preparation of both enantiomers of 1 via a single synthetic route. This leads to uneconomical use of material. Compared to the reported method of Masamune,[8] which is limited to the formation of the (2R,5R)-enantiomer, the accessibility of both enantiomers of 1 is an advantage of the present route.

The present methodology offers an alternative to the Schlessinger procedure.[6] A distinct advantage concerns the few reaction steps that are necessary to prepare enantiomerically pure **1**, in particular when relatively small amounts of material are required in a short period of time.

Experimental Section

General remarks

Melting points (uncorrected) were determined on a Mettler FP-2 melting point apparatus, equipped with a Mettler FP-21 microscope. ^{1}H-NMR spectra were recorded on a Varian Gemini 200 (at 200 MHz), or a Varian VXR-300 spectrometer (at 300 MHz). Chemical shifts are denoted in δ-units (ppm) relative to the solvent and converted to the TMS scale using δ ($CDCl_3$) = 7.26 ppm. ^{13}C-NMR spectra were recorded on a Varian Gemini 200 (at 50.32 MHz), or a Varian VXR-300 spectrometer (at 75.48 MHz). Chemical shifts are denoted in δ-units (ppm) relative to the solvent and converted to the TMS scale using δ ($CDCl_3$) = 76.91 ppm. The splitting patterns are designated as follows: s (singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), m (multiplet), and br (broad). Mass spectra were recorded on a AEI-MS-902 mass spectrometer by EI (acc. voltage 8 kV, voltage 70 eV). Rotations are measured on a Perkin Elmer 241 MC polarimeter at room temperature at the NaD-line. Elemental analyses were performed in the Microanalytical Department of this laboratory. The X-ray data collection was performed on a Nonius CAD4F-diffractometer equipped with a graphite monochromator and interfaced to a VAX-11/730 computer. Gas chromatography was performed on a Hewlet Packard 5890 gas chromatograph. All reagents and solvents were purified and dried if necessary, according to standard procedures. (S)-α-methylbenzylamine was purchased from Janssen and 2,5-hexanediol was purchased from Eastman Kodak.

2,5-Hexanediol dimethanesulfonate 3

To a solution of 48.74 g (0.41 mol) 2,5-hexanediol **2** in 500 ml CH_2Cl_2 was added 143 ml (1.02 mol) triethylamine. After cooling the solution to -20°C 70.3 ml (0.91 mol) of methanesulfonyl chloride was added under vigorous stirring, at such a rate that the temperature did not exceed -20°C. After addition of the methanesulfonyl chloride (1 hr), the suspension was allowed to warm to 0°C and poured into 400 ml 1N HCl. The organic layer was separated, and the aqueous layer was extracted three times with portions of 250 ml CH_2Cl_2. The combined organic layers were washed with 300 ml saturated $NaHCO_3$ solution, dried over Na_2SO_4 and the solvent was removed in vacuo. There was obtained 106.55 g (0.39 mol, 94%) off white solid as a mixture of diastereoisomers. The crude product **3** was dissolved in boiling MeOH and **3b** was allowed to crystallize to provide 52.34 g of white crystals (49%, mp=88-93°C). ^{13}C-NMR showed that the material existed for 89% of **3b**. Concentration of the mother liquor yielded 54.21 g brownish oil (51%), which consisted for 87% of **3a** and for 13% of **3b**. The crude oil was used directly in the next step, without further purification.

^{1}H-NMR (300 MHz, $CDCl_3$); δ 1.40 (d, 6H, J=6.2 Hz), 1.71-1.81 (m, 4H), 2.99 (s, 6H), 4.80-4.86 (m, 2H). ^{13}C-NMR (300 MHz, $CDCl_3$); δ 20.97 (q), 31.77 (t), 38.49 (q), 78.70 (d). Signals of **3b** appeared at 32.05 (t) and 79.03 (d) ppm. These data were similar to those reported in literature.[8]

(S)-2'-Phenyl-N-ethyl-2,5-dimethylpyrrolidine 4a-c

52.59 g (0.19 mol) crude 3a and 69.5 g (0.57 mol) (S)-α-methylbenzylamine were heated to 60°C for 18 hours. The reaction was followed by ^{1}H-NMR until completion. The reaction mixture was poured in 250 ml 2N NaOH and extracted three times with portions of 100 ml pentane. The organic layer was dried over Na_2SO_4 and the solvent was evaporated. The excess of (S)-α-methylbenzylamine was removed by fractional distillation (bp 75°C, 14 mmHg). The product was purified by distillation (bp 67°C, 0.05 mmHg). After removal of traces of α-methylbenzylamine by chromatography (silicagel, petroleum ether/ether 10:1) 26.25 g of 4a-c (68%) was collected as a clear oil. The product consisted of a mixture of three diastereomers 4a (36%), 4b (33%) and 4c (31%) as determined by integration of the pyrrolidine methyl groups in the ^{1}H-NMR spectrum. GC analysis (at 170°C over an apolar capillary column 15 m x 0.53 mm x 2.65μm film thickness; retention times for 4a, 4b and 4c are respectively 6.59, 6.38 and 5.77 min) gave identical results.

^{1}H-NMR (300 MHz, $CDCl_3$); 4a δ 0.72 (d, 6H, J=6.2 Hz), 1.32-1.47 (m, 2H), 1.45 (d, 3H, J=6.6 Hz), 2.04-2.13 (m, 2H), 3.19-3.27 (m, 2H), 3.72 (q, 1H, J=6.6 Hz), 7.20-7.43 (m, 5H). 4b δ 0.99 (d, 6H, J=6.2 Hz), 1.27-1.43 (m, 2H), 1.35 (d, 3H, J=6.6 Hz), 2.04-2.13 (m, 2H), 3.09-3.19 (m, 2H), 3.86 (q, 1H, J=6.6 Hz), 7.20-7.43 (m, 5H). 4c δ 0.91 (d, 3H, J=5.9 Hz), 1.08 (d, 3H, J=6.2 Hz), 1.27-1.43 (m, 2H), 1.44 (d, 3H, J=7.0 Hz), 1.63-1.76 (m, 2H), 2.87-2,98 (m, 1H), 2.98-3.09 (m, 1H), 3.97 (q, 1H, J=7.0 Hz), 7.20-7.43 (m, 5H). ^{13}C-NMR (300 MHz, $CDCl_3$); 4a δ 18.77 (q), 21.94 (q), 31.22 (t), 55.39 (d), 58.81 (d), 126.66 (d), 127.82 (d), 128.03 (d), 146.22 (s). 4b δ 20.66 (q), 25.51 (q), 31.40 (t), 54.97 (d), 55.09 (d), 126.02 (d), 126.08 (d), 127.03 (d), 147.44 (s). 4c δ 17.03 (q), 22.55 (q), 23.41 (q), 31.89 (t), 32.50 (t), 55.70 (d), 56.40 (d), 57,28 (d), 126.23 (d), 127.61 (d), 128.19 (d), 144.58 (s). HRMS: m/e calcd for $C_{14}H_{21}N$ 203.176, found 203.167. Anal. Calcd for $C_{14}H_{21}N$: C, 82.70; H, 10.41; N, 6.89. Found: C, 82.41; H, 10.47; N, 6.89.

(S)-2'-Phenyl-N-ethyl-2,5-dimethylpyrrolidine, picrate 5

25.00 g (0.12 mol) of 4 was dissolved in 50 ml MeOH and the solution was added to a saturated solution of 30.20 g picric acid (0.13 mol) in MeOH. To induce crystallization some benzene or a crystal of 5 was added. After crystallization overnight, yellow crystals (28.21 g, 54%) were obtained. GC analysis of the released amine showed that it contained 57% of diastereomer 4a. The solid was recrystallized 4 times from methanol, until GC analysis of the released amine showed the presence of only one diastereomer. Pure 5 (5.01 g, 27%) was obtained as clear yellow crystals, mp 177 °C, d.e. ≥ 99.7%. Concentration of the combined mother liquors and recrystallization of the solid yielded two more crops of respectively 3.10 g (17%) and 1.45 g (9%) of 5.

$[\alpha]_D^{20}$ -5.61 (c 3.2, acetone), ^{1}H-NMR (200 MHz, d^6-DMSO); δ 0.40 (d, 3H, J=6.5 Hz), 1.34 (d, 3H, J=6.8 Hz), 1.41-1.58 (m, 1H), 1.62 (d, 3H, J=6.6 Hz), 1.75-1.92 (m, 1H), 1.95-2.07 (m, 1H), 2.27-2.42 (m, 1H), 3.60-3.68 (m, 1H), 4.08-4.20 (m, 1H), 4.22-4.35 (m, 1H), 7.44-7.52 (m, 3H), 7.57-7.63 (m, 2H), 8.59 (s, 2H), 9.01 (br s, 1H). ^{13}C-NMR (300 MHz, DMSO); δ 12.81 (q), 18.98 (q), 19.34 (q), 29.04 (t), 30.14 (t), 59.85 (d), 60.12 (d), 60.96 (d), 124.12 (s), 125.16 (d), 128.77 (d), 129.59 (d), 136.84 (s), 141.86 (d), 160.78 (s). MS: no M^+-peak. Anal. Calcd. for $C_{20}H_{24}N_4O_7$: C, 55.55; H, 5.59; N, 12.96. Found: C, 55.46; H, 5.48; N 12.74.

Crystal structure determination of 5

A suitable crystal of compound **5** was obtained by crystallization from methanol via slow evaporation of the solvent. A transparent yellow prismatic crystal of dimensions 0.15 x 0.20 x 0.45 mm. was glued on top of a glass fiber and transferred to goniometer of an Enraf-Nonius CAD-4F diffractometer, interfaced to a VAX-11/730 computer. Single-crystal diffraction data were collected at room-temperature (295 K), with the use of graphite-monochromated Mo $K\bar{\alpha}$ radiation (λ = 0.71073 Å). The compound crystallized in the monoclinic space group $P2_1$. The monoclinic cell parameters and volume are: a = 8.133(1), b = 11.651(1), c = 22.575(2) Å, β = 95.962(8)°, V = 2127.6(4) Å^3. For Z = 4 and FW = 423.43 the calculated density is 1.350 g cm^{-3}. μ = 1.0 cm^{-1}, F(000) = 912, R_F = 0.076 for 3089 unique observed reflections with I $\geq$ 1.5 σ(I) and 565 parameters. The structure was solved by direct methods with SHELXS86.[19] The hydrogen atoms attached to N(4) and N(8), respectively, involved in hydrogen bonding, could be identified in a difference Fourier map. However, in view of the unfavorable data to parameter ratio only these H atoms attached to N were refined. All other H atoms were introduced at calculated positions (C-H = 0.96 Å) and refined in the riding mode on their carrier atoms with an isotropic thermal displacement parameter common to all H atoms. The absolute structure is based on the known absolute configuration of (S)-α-methylbenzylamine, the synthesis route as described, and the relative configuration as determined by this X-ray analysis. Two crystallographically independent molecules of the title compound are present in the asymmetric unit. The crystal structure consist of molecules of an anion and cation connected by a hydrogen bond.

Scattering factors were taken from Cromer & Mann.[20] Anomalous dispersion factors taken from Cromer & Liberman[21] were included in F_C. All calculations were carried out on the CDC-Cyber 962-31 computer of the University of Groningen with the program packages XTAL,[22] PLATON[23] (calculation of geometric data) and a locally modified version of the program PLUTO[24] (preparation of illustrations).

(S)-2'-Phenyl-N-ethyl-(2S,5S)-dimethylpyrrolidine 4a

8.87 g (20.5 mmol) of **5** was dissolved in 300 ml of 2N NaOH under slight heating. After cooling, the water layer was extracted three times with pentane (100 ml). The combined organic extracts were dried over Na_2SO_4. After removing the solvent 3.58 g (17.6 mmol, 86%) of **4a** was obtained and was used without further purification. GC analysis (at 170°C, over an apolar capillary column, 15 m x 0.53 mm x 2.65 μm, retention time for **4a** 6.59 min) indicated a diastereomeric purity $\geq$ 99.7%.

$[\alpha]_D^{20}$ -8.74 (c 1.5, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$); δ 0.74 (d, 6H, J=6.3 Hz), 1.27-1.43 (m, 2H), 1.47 (d, 3H, J=6.5 Hz), 2.00-2.20 (m, 2H), 3.19-3.33 (m, 2H), 3.73 (q, 1H, J=6.5 Hz), 7.20-7.44 (m, 5H). ^{13}C-NMR; (200 MHz, $CDCl_3$); δ 18.86 (q), 22.05 (q), 31.30 (t), 55.51 (d), 58.98 (d), 126.80 (d), 127.95 (d), 128.17 (d), 146.36 (s).

Trans-(2S,5S)-dimethylpyrrolidine 1

3.11 g (15 mmol) **4a** was dissolved in 25 ml glacial acetic acid. After addition of 1.2 g of Pd/C (10%) the reaction mixture was shaken in a parr bottle for 36 hours at room temperature under 50 psi H_2 pressure. The Pd/C was removed after filtration over celite. The catalyst was washed two times with 5 ml methanol. The methanol was removed by evaporation at 0 °C and 1 mmHg. To the solution was

added subsequently 50 ml water and 30 ml ether followed by the dropwise addition at 0°C of 25 ml 50% NaOH solution. The salts were filtrated and washed with 10 ml ether. The ether layer was removed and the alkaline water layer was extracted two times with 30 ml ether. The combined ether layers were dried over KOH and the solvent was removed by distillation. The remaining oil was distilled at 100°C and acidified with ether/HCl. The ether and traces of ethylbenzene were removed at the rotary evaporator. The HCl salt of 1 was collected as a white solid and dried in a vacuum oven (1.10 g, 8.1 mmol, 53%). m.p. 204.1-204.9, e.e. ≥ 97%,[15] $[\alpha]_D^{RT}$ -5.52 (c 1.05, CH_2Cl_2) [lit;[8] mp 200-203°C, $[\alpha]_D^{20}$ +5.57 (c 3.0, CH_2Cl_2) for the (2R,5R) enantiomer) HCl-salt of 1. ^{1}H-NMR (200 MHz, $CDCl_3$); δ 1.44 (d, 6H, J=6.7 Hz), 1.49-1.70 (m, 2H), 2.03-2.23 (m, 2H), 3.67-3.81 (m, 2H), 9.30-9.40 (br s, 2H). ^{13}C-NMR (200 MHz, $CDCl_3$); δ 18.03 (q), 32.15 (t), 54.84 (d).

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