A Straightforward Synthesis of Enantiomerically Pure *trans*-2,5-Bis(alkyloxymethyl) pyrrolidines by 1,3-Dipolar Cycloaddition Reactions of Azomethine Ylides [1])

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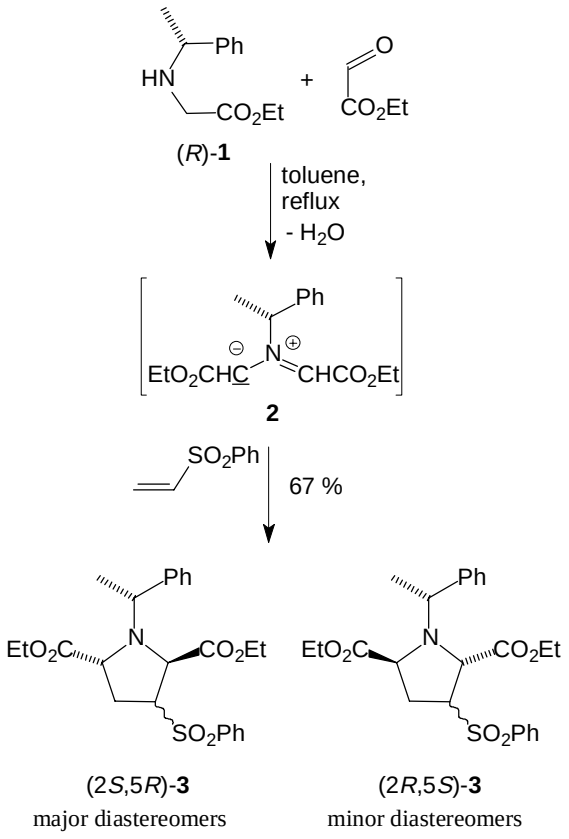
Abstract. A new efficient method for the stereoselective preparation of *trans*-2,5-bis(alkyloxymethyl)pyrrolidines (**7**) using easily available starting materials is described. The main step of this synthesis is the stereoselective formation of the pyrrolidine ring by the 1,3-dipolar cycloaddition reaction of an *in situ* generated azomethine ylide. Both enantiomers of the C_2-symmetric auxiliaries are prepared separately in a short reaction sequence.

2,5-Disubstituted pyrrolidine derivatives with a C_2 axis of symmetry are versatile chiral auxiliaries in asymmetric synthesis [1–3]. *Trans*-2,5-bis(alkyloxymethyl)pyrrolidines **7** especially are very powerful auxiliaries and the development of new efficient syntheses for these substances is of current interest. The corresponding diacid is a natural product which has been isolated from the red alga *schizymenia dubyi* [4].

The first synthesis of enantiomerically pure *trans*-2,5-bis(alkyloxymethyl)pyrrolidines **7** by optical resolution was published by Katsuki *et al*. [5] This method, starting from 2,5-dibromoadipate and dibenzylamine, was optimized by Ghozes *et al*. [6]. Later on, Yamamoto *et al*. [7] and Durst *et al*. [8] improved this synthesis by using chiral auxiliaries. Additional preparations have been reported in the last few years which started from optically active *D*-mannitol [9, 10], (*S*)-*O*-benzylglycidol [11], $\Delta^{4,5}$oxazolidin-2-one [12, 13] or L-serine [14]. Most of these methods are based on long reaction sequences or require starting materials which are expensive or difficult to obtain.

During our investigations on iminium salts and 1,3-dipolar cycloaddition reactions of azomethine ylides [15] we developed an efficient one-pot reaction for the stereoselective preparation of highly substituted pyrrolidines [16, 17]. The *in situ* generation of azomethine ylides from secondary benzylic amines and aldehydes *via* iminium salts, followed by the cycloaddition with different dipolarophiles gives rise to a wide variety of 2,5-dicarboxylated and 2,5-diphenyl-substituted pyrrolidines. Using optically pure 1-phenylethylamine as a chiral template, enantiomerically pure 2,3,4,5-tetrasubstituted proline derivatives have already been synthesized by this method [17].

We now describe a new and short reaction sequence for the synthesis of enantiomerically pure *trans*-2,5-bis(alkyloxymethyl)pyrrolidines **7** which includes the 1,3-dipolar cycloaddition reaction of an azomethine ylide to phenylvinylsulfone [18, 19] as an ethene equivalent. This method allows the stereoselective formation of the pyrrolidine ring by a simple one-pot reaction using easily available and inexpensive starting materials.



Scheme 1 Mixture of cycloadducts **3** with d.r. = 38 : 35 : 17 : 10

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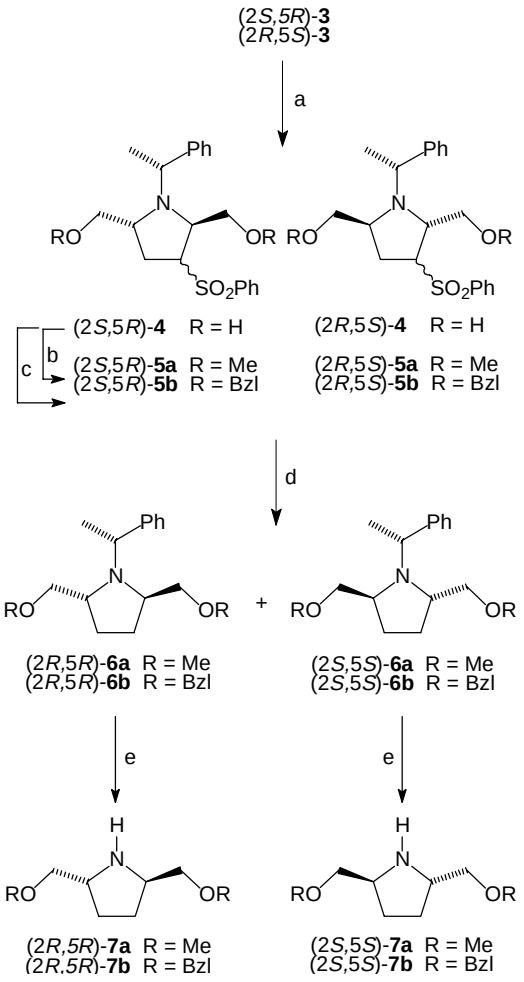
The one-pot reaction of ethyl *N*-((*R*)-**1**-phenylethyl) glycinecarboxylate ((*R*)-**1**) and ethyl glyoxalate with phenylvinylsulfone as the dipolarophile in refluxing toluene, with azeotropic removal of water, yielded a diastereomeric mixture of the pyrrolidines **3** with d.r. = 38:35:17:10 (Scheme 1). These cycloadducts are formed by an *exo*- and an *endo*-attack of the dipolarophile on the *in situ* generated *anti*-azomethine ylide **2**. Using an excess of amine (*R*)-**1** and glyoxalate to reach a total conversion of the sulfone, we also obtained small amounts of oxazolidine as a by-product, which results from the cycloaddition of ethyl glyoxalate to the ylide **2**. The cycloaddition products were purified by column chromatography to yield 67% of the mixture of pyrrolidines **3**. These diastereomers were not separated, because it is more efficient to carry out the following reaction steps with the diastereomeric mixture of the cycloadducts **3**.



Scheme 2 a: $LiAlH_4$, 91%; b: NaH, MeI, 95%; c: NaH, Bzl-Br, 84%; d: 1. Na-Hg (10%), Na_2HPO_4, THF/MeOH; 2. chromatography; e: R = Me: H_2, 10% Pd/C, quant.; R = Bzl: H_2, 20% $Pd(OH)_2$/C, 90%.

The reduction of the pyrrolidines **3** with $LiAlH_4$ in THF led to the diols **4** in 91% yield. These products were transformed into the ethers **5** without prior purification. At this step of the synthesis different protecting groups of the hydroxy function can be introduced into the molecule. We prepared the methyl ethers **5a** by the reaction of the diols **4** with sodium hydride and methyl iodide in THF. The use of benzyl bromide gave rise to the dibenzylic ethers **5b**. In the latter case column chromatography was necessary to remove the excess of benzyl bromide, but the desulfonation that followed was also carried out successfully if the benzyl bromide was removed *in vacuo*, as far as possible.

The reductive desulfonation of **5a** with 10% Na–Hg in THF/MeOH, using Na_2HPO_4 as buffer, yielded the 2,5-disubstituted *N*-protected pyrrolidines **6a**. The two diastereomers were separated by column chromatography to give 48% of the major diastereomer (2*R*,5*R*)-**6a** and 14% of the minor diastereomer (2*S*,5*S*)-**6a**. The purity of the isolated fractions was determined by GC using a chiral column (HYDRODEX β-PM). The absolute configuration was proved by the determination of the optical rotation and comparison with the values reported in literature [7]. Using the same procedure the benzylic ethers **5b** were desulfonated to yield 39% of (2*R*,5*R*)-**6b** and 10% of (2*S*,5*S*)-**6b**.

The debenzylation of the *N*-protected auxiliaries **6** by heterogeneous catalysed hydrogenolysis offered the enantiomerically pure pyrrolidines **7**. **6a** was debenzylated by a standard method using 10% Pd/C as catalyst. Selective *N*-debenzylation of the benzylic ethers **6b** was achieved with Pearlman´s catalyst (20% $Pd(OH)_2$/C) [9, 20].

In conclusion, we have developed an efficient reaction sequence for the synthesis of *trans*-2,5-bis(alkyloxymethyl)pyrrolidines **7**, which is also suitable for the preparation of larger amounts of these important auxiliaries. The 1,3-dipolar cycloaddition reaction of the *in situ* generated azomethine ylide **2** allows the stereoselective formation of the pyrrolidine ring by a simple one-pot reaction. As the separation of the diastereomeric cycloadducts was carried out just before the last step of the synthesis, both enantiomers of the auxiliaries **7** were obtained in a single reaction sequence.

By starting the synthesis with (*S*)-**1** as the amine we obtained the auxiliaries (2*S*,5*S*)-**7** as major products and (2*R*,5*R*)-**7** as minor products.

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Experimental

Ethyl *N*-(1-phenylethyl)glycine carboxylate (**1**) [21] was syn-

thesized according to literature procedures. Anhydrous THF was freshly distilled from sodium under argon. Petroleum ether refers to the fraction with *b.p.* 50–70 °C. Column chromatography on silica gel was performed with Merck Kieselgel 60 (0.040–0.063 mm). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ARX 200 or a Bruker AMX 300 spectrometer, using TMS as internal standard. IR spectra were recorded on a Nicolet 510 P FT-IR spectrometer. GC/MS data were obtained from a Finnigan MAT Magnum System 240 and MS data from a VG Fisons Autospec. Specific optical rotations were measured with a Perkin Elmer 241 polarimeter using a 1.00 dm cell. Elemental analyses were performed on a Perkin Elmer 240 Elemental Analyzer. Microanalyses were in satisfactory agreement with the calculated values: C ± 0.31, H ± 0.23, N ± 0.22.

2,5-Diethyl 1-(1-Phenylethyl)-3-phenylsulfonylpyrrolidine-2,5-dicarboxylate (**3**)

A solution of amine **1** (1.55 g, 7.5 mmol), ethyl glyoxalate (2.0 mL, 10.0 mmol; 50% in toluene) and phenyl vinyl sulfone (0.84 g, 5.0 mmol) in toluene (20 mL) was refluxed for 2 d under Dean-Stark conditions. After removal of the solvent under reduced pressure the crude product was purified by column chromatography (silica gel; petroleum ether/EtOAc, 80:20) to yield 1.54 g (67%) of the diastereomers **3** as a yellowish oil. The diastereomeric mixture is used for the next reaction step without further purification.

Diastereomeric Mixture of **3**

IR (film): ν/cm^{-1} = 2979, 1733, 1447, 1150. – ^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm = 1.04–1.41 (m, $CO_2CH_2C\underline{H}_3$, NCHC$\underline{H}_3$), 2.43–3.03 (m, 4-H), 3.67–4.33 (m, 2-H, 3-H, 5-H, $CO_2C\underline{H}_2CH_3$, N$\underline{C}$HCH$_3$), 7.19–7.28 (m, H$_{arom}$), 7.45–7.66 (m, H$_{arom}$), 7.79–7.91 (m, H$_{arom}$). – ^{13}C NMR (75 MHz, $CDCl_3$): δ/ppm = 13.31–13.97 ($CO_2CH_2\underline{C}H_3$), 21.78–22.95 (NCH$\underline{C}$H$_3$), 29.10–30.53 (C-4), 57.47–66.71 (C-2, C-3, C-5, $CO_2\underline{C}H_2CH_3$, N$\underline{C}$HCH$_3$), 126.60–144.02 (C$_{arom}$), 169.66–175.17 (C=O). MS (70 eV): *m/z* (%) = 386 (16, M$^+$–$CO_2C_2H_5$), 318 (6, M$^+$–SO_2Ph), 282 (18), 216 (11), 140 (19), 105 (100).

$C_{24}H_{28}NO_6S$	Calcd.:	C 62.86	H 6.16	N 3.06
(458.16)	Found:	C 63.11	H 5.97	N 3.27.

2,5-Bis(hydroxymethyl)-1-(1-phenylethyl)-3-phenylsulfonylpyrrolidine (**4**)

Under argon a solution of the diastereomeric mixture of **3** (1.54 g, 3.27 mmol) in anhydrous THF (40 mL) was cooled to 0 °C, $LiAlH_4$ (0.23 g, 6 mmol) was added, and the mixture was stirred for 3 h at r.t. H_2O was added carefully at 0 °C to destroy the excess of $LiAlH_4$. The solid was separated by filtration and washed with EtOAc several times. The filtrate was dried ($MgSO_4$), and concentrated under reduced pressure to yield 1.26 g (quant.) of the diastereomers **4** as a yellow viscous oil.

Major Diastereomers **4**

^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm = 1.42 (d, 3H, NCH-C$\underline{H}_3$), 1.49 (d, 3H, NCHC$\underline{H}_3$), 2.24–2.36 (m, 4H, 4-H), 3.10 (br. s, OH), 3.28–3.86 (m, 14H, 2-H, 3-H, 5-H, C$\underline{H}_2$OH), 4.14 (q, 1H, NC$\underline{H}$CH$_3$), 4.22 (q, 1H, NC$\underline{H}$CH$_3$), 7.18–7.37 (m, 10H, H$_{arom}$), 7.48–7.67 (m, 6H, H$_{arom}$), 7.82–7.92 (m, 4H, H$_{arom}$). – ^{13}C NMR (75 MHz, $CDCl_3$): δ/ppm = 17.42, 18.81 (NCH$\underline{C}$H$_3$), 27.56, 28.75 (C-4), 53.96, 54.38 (N$\underline{C}$H-CH$_3$), 59.30 (CH), 60.53 (CH$_2$), 61.21 (CH), 61.50 (CH$_2$), 62.05 (CH$_2$), 62.45 (CH), 62.51 (CH$_2$), 63.79, 64.57 (CH), 126.45, 126.88, 127.27, 127.33, 128.35, 128.46, 128.57, 129.11, 129.20, 133.66, 133.73, 137.77, 137.89, 142.20, 145.23 (C$_{arom}$).

$C_{20}H_{25}NO_4S$	Calcd.:	C 63.97	H 6.71	N 3.73
(375.15)	Found:	C 64.25	H 6.34	N 3.54.

Mixture of all Diastereomers **4**

IR (Film): ν/cm^{-1} = 3373, 2937, 1446, 1032. – MS (70 eV): *m/z* (%) = 344 (11, M$^+$–CH$_2$OH), 240 (6), 220 (6), 202 (4), 105 (100).

2,5-Bis(methoxymethyl)-1-(1-phenylethyl)-3-phenylsulfonylpyrrolidine (**5a**)

A solution of the diastereomeric mixture of **4** (1.25 g, 3.3 mmol) in anhydrous THF (20 mL) and MeI (2.55 g, 17.9 mmol) was added slowly to a suspension of NaH (0.52 g, 17.9 mmol; 80%, washed with anhydrous *n*-Hexane) in anhydrous THF (10 mL) at 0 °C. The mixture was stirred for 2 h at r.t. and cooled to 0 °C before H_2O was added carefully. The solid was separated by filtration and the filtrate extracted with Et_2O (3 × 30 mL). The organic layer was washed with brine (2 × 30 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure to yield 1.25 g (95%) of the diastereomers **5a** as a yellowish oil.

Major Diastereomers **5a**

^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm = 1.33 (d, 3H, NCH–C$\underline{H}_3$), 1.39 (d, 3H, NCHC$\underline{H}_3$), 1.98–2.42 (m, 4H, 4-H), 3.01–3.72 (m, 14H, 2-H, 3-H, 5-H, CH$_2$O), 3.06 (s, 6H, OCH$_3$), 3.14 (s, 3H, OCH$_3$), 3.15 (s, 3H, OCH$_3$), 4.01–4.15 (m, 2H, NC$\underline{H}$CH$_3$), 7.14–7.32 (m, 10H, H$_{arom}$), 7.48–7.60 (m, 6H, H$_{arom}$), 7.81–7.89 (m, 4H, H$_{arom}$). – ^{13}C NMR (75 MHz, $CDCl_3$): δ/ppm = 18.20, 20.44 (NCH$\underline{C}$H$_3$), 30.00, 30.93 (C-4), 55.29, 58.73, 59.04, 59.17, 59.25, 59.37, 59.96, 61.88, 64.95, 65.98 (CH, CH$_3$), 72.91, 73.11, 75.05, 76.44 (CH$_2$O), 126.75, 127.14, 127.25, 127.94, 128.39, 128.43, 129.19, 129.33, 129.43, 133.81, 138.36, 143.05, 145.84 (C$_{arom}$).

$C_{22}H_{29}NO_4S$	Calcd.:	C 65.48	H 7.25	N 3.47
(403.18)	Found:	C 65.24	H 7.45	N 3.69.

Mixture of all Diastereomers **5a**

IR (film): ν/cm^{-1} = 2859, 1450, 1182. – MS (70 eV): *m/z* (%) = 358 (29, M$^+$–CH$_2$OCH$_3$), 254 (18), 216 (5), 105 (100).

2,5-Bis(benzyloxymethyl)-1-(1-phenylethyl)-3-phenylsulfonyl-pyrrolidine (**5b**)

5b was prepared in accordance to the preparation of **5a** starting from the diastereomeric mixture of **4** (0.43 g, 1.2 mmol), benzyl bromide (0.59 g, 3.5 mmol) and NaH (0.19 g, 6.5 mmol; 80%, washed with anhydrous *n*-Hexane) to yield 0.51 g (84%) of the diastereomers **5b**. For the preparation of **6b** it is sufficient to remove the excess of benzyl bromide *in vacuo* as far as possible. Otherwise the crude product can be purified by

column chromatography (silica gel; petroleum ether/EtOAc, 70:30).

Mixture of all Diastereomers **5b**

IR (film): ν/cm^{-1} = 2 857, 1 452, 1 186, 1 029. – ^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm = 1.22–1.36 (m, NCHC$\underline{H}_3$), 2.15–2.60 (m, 4-H), 3.02–3.79 (m), 3.98–4.15 (m), 4.19–4.61 (m), 7.16–7.85 (m, H_{arom}). – ^{13}C NMR (75 MHz, $CDCl_3$): δ/ppm = 17.75, 20.72 (NCH$\underline{C}H_3$), 29.69, 30.51 (C-4), 54.67, 55.15 (N$\underline{C}HCH_3$), 58.44, 59.08, 59.68, 61.60, 64.72, 65.98 (C-2, C-3, C-5), 69.85, 70.02, 72.53, 72.84, 73.00, 73.88 (CH_2O, OCH_2Ph), 126.27–133.48, 137.62–133.24 (C_{arom}). – MS (70 eV): *m/z* (%) = 434 (52, M^+–$PhCH_2OCH_2$), 330 (31), 188 (22), 158 (22), 105 (83), 91 (100).

$C_{34}H_{37}NO_4S$	Calcd.:	C 73.48	H 6.72	N 2.52
(555.24)	Found:	C 73.36	H 6.95	N 2.34.

2,5-Bis(methoxymethyl)-1-(1-phenylethyl)-pyrrolidine (**6a**) [7]

Under argon Na_2HPO_4 (0.72 g, 6.1 mmol) was added to a solution of the sulfone **5a** (1.1 g, 2.75 mmol) in anhydrous THF (15 mL) and anhydrous MeOH (10 mL). The suspension was cooled to 0 °C and 10% Na–Hg (3.25 g, 14 mmol Na) was added. After stirring at r.t. over night the liquid was decanted and the solid washed with Et_2O several times. The combined organic layers were washed with H_2O (2 × 30 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the crude product purified by column chromatography (silica gel; petroleum ether/EtOAc, 90:10) to yield 0.35 g (48%) of (2*R*,5*R*)-**6a**, 0.1 g (14%) of (2*S*,2*S*)-**6a** and 0.12 g (18%) of a mixture of both diastereomers **6a**.

(1'R,2R,5R)-2,5-Bis(methoxymethyl)-1-(1-phenylethyl)-pyrrolidine ((**2R,5R**)-**6a**)

$[\alpha]_D^{20}$ = + 68.1° (*c* = 1.4, CH_2Cl_2). – IR (film): ν/cm^{-1} = 2 924, 2 875, 1 451, 1 120. – ^{1}H NMR (200 MHz, $CDCl_3$): δ/ppm = 1.36 (d, *J* = 6.7 Hz, 3H, NCHC$\underline{H}_3$), 1.66–2.08 (m, 4H, 3-H, 4-H), 3.09–3.37 (m, 6H, 2-H, 5-H, $2CH_2O$), 3.23 (s, 6H, 2 OCH_3), 4.02 (q, *J* = 6.7 Hz, 1H, NC$\underline{H}CH_3$), 7.13–7.37 (m, 5 H, H_{arom}). – ^{13}C NMR (75 MHz, $CDCl_3$): δ/ppm = 24.75 (NCH$\underline{C}H_3$), 27.15 (C-3, C-4), 57.66 (N$\underline{C}HCH_3$), 58.69, 58.78 (C-2, C-5, $2OCH_3$), 75.19 ($2CH_2O$), 126.20, 126.69, 127.94, 146.83 (C_{arom}). – GC/MS (80 eV, 220 °C): *m/z* (%) = 263 (40, M^+), 231 (12), 218 (100), 114 (83), 105 (74).

$C_{16}H_{25}NO_2$	Calcd.:	C 72.95	H 9.57	N 5.32
(263.19)	Found:	C 72.65	H 9.77	N 5.49.

(1'R,2S,5S)-2,5-Bis(methoxymethyl)-1-(1-phenylethyl)-pyrrolidine ((**2S,5S**)-**6a**)

$[\alpha]_D^{20}$ = – 42.7° (*c* = 1.2, CH_2Cl_2). – IR (film): ν/cm^{-1} = 2 929, 1 436, 1 031. – ^{1}H NMR (200 MHz, $CDCl_3$): δ/ppm = 1.49 (d, *J* = 6.5 Hz, 3H, NCHC$\underline{H}_3$), 1.59–2.98 (m, 4H, 3-H, 4-H), 2.87–3.05 (m, 4H), 3.16 (s, 6H, $2OCH_3$), 3.17–3.36 (m, 2H), 3.95 (q, *J* = 6.5 Hz, 1H, NCHC$\underline{H}_3$), 7.23–7.38 (m, 5H, H_{arom}). – ^{13}C NMR (75 MHz, $CDCl_3$): δ/ppm = 21.01 (NCH–$\underline{C}H_3$), 26.86 (C-3, C-4), 57.49 (N$\underline{C}HCH_3$), 58.60, 59.22 (C-2, C-5, $2OCH_3$), 73.75 ($2CH_2O$), 126.86, 127.89, 145.09 (C_{arom}). – GC/MS (80 eV, 220 °C): *m/z* (%) = 263 (42, M^+), 231 (12), 217 (100), 114 (80), 105 (72).

$C_{16}H_{25}NO_2$	Calcd.:	C 72.95	H 9.57	N 5.32
(263.19)	Found:	C 73.11	H 9.42	N 5.13.

2,5-Bis(benzyloxymethyl)-1-(1-phenylethyl)-pyrrolidine (**6b**)

6b was prepared in accordance to the preparation of **6a** starting from **5b** (0.51 g, 0.9 mmol) to yield 0.15 g (39%) of the major diastereomer (2*R*,5*R*)-**6b** and 0.04 g (10%) of the minor diastereomer (2*S*,2*S*)-**6b** as colourless viscous oils.

(1'R,2R,5R)-2,5-Bis(benzyloxymethyl)-1-(1-phenylethyl)-pyrrolidine ((**2R,5R**)-**6b**)

$[\alpha]_D^{20}$ = + 58.7° (*c* = 1.1, $CHCl_3$). – IR (film): ν/cm^{-1} = 2 855, 1 454, 1 099, 1 029. – ^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm = 1.29 (d, *J* = 6.6 Hz, 3H, NCHC$\underline{H}_3$), 1.81–1.88 (m, 2H, 3-H, 4-H), 2.05–2.10 (m, 2H, 3-H, 4-H), 3.24–3.26 (m, 4H, 2 CH_2O), 3.35–3.43 (m, 2H, 2-H, 5-H), 3.98 (q, *J* = 6.6 Hz, 1H, NC$\underline{H}CH_3$), 4.43 (s, 4H, OCH_2Ph), 7.25–7.35 (m, 15H, H_{arom}). – ^{13}C NMR (75 MHz, $CDCl_3$): δ/ppm = 25.02 (NCH–$\underline{C}H_3$), 27.55 (C-3, C-4), 57.80 (N$\underline{C}HCH_3$), 59.07 (C-2, C-5), 72.82, 72.97 ($2CH_2O$, $2OCH_2Ph$), 126.20, 126.73, 127.28, 127.35, 128.00, 128.17, 138.56, 146.91 (C_{arom}).

$C_{28}H_{33}NO_2$	Calcd.:	C 80.91	H 8.00	N 3.37
(416.25)	Found:	C 81.03	H 8.20	N 3.57.

(1'R,2S,5S)-2,5-Bis(benzyloxymethyl)-1-(1-phenylethyl)-pyrrolidine ((**2S,5S**)-**6b**)

$[\alpha]_D^{20}$ = – 34.7° (*c* = 1.0, $CHCl_3$). – IR (film): ν/cm^{-1} = 2 855, 1 454, 1 099, 1 029. – ^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm = 1.44 (d, *J* = 6.5 Hz, 3H, NCHC$\underline{H}_3$), 1.77–1.83 (m, 2H, 3-H, 4-H), 1.91–1.98 (m, 2H, 3-H, 4-H), 3.01–3.14 (m, 4H, 2 CH_2O), 3.23–3.28 (m, 2H, 2-H, 5-H), 3.95 (q, *J* = 6.5 Hz, 1H, NC$\underline{H}CH_3$), 4.32 (s, 4H, OCH_2Ph), 7.20–7.34 (m, 15H, H_{arom}). – ^{13}C NMR (75 MHz, $CDCl_3$): δ/ppm = 20.88 (NCH–$\underline{C}H_3$), 27.05 (C-3, C-4), 57.29 (N$\underline{C}HCH_3$), 59.27 (C-2, C-5), 71.53, 72.87 ($2CH_2O$, $2OCH_2Ph$), 126.85, 127.21, 127.31, 127.86, 127.91, 128.09, 128.18, 138.42, 144.99 (C_{arom}).

$C_{28}H_{33}NO_2$	Calcd.:	C 80.91	H 8.00	N 3.37
(416.25)	Found:	C 80.60	H 8.23	N 3.58.

(2R,5R)-2,5-Bis(methoxymethyl)pyrrolidine ((**2R,5R**)-**7a**) [7]

A solution of (2*R*,5*R*)-**6a** (0.3 g, 1.14 mmol) in anhydrous EtOH (20 mL) was stirred at r.t. in the presence of 10% Pd/C (0.06 g) and hydrogen was bubbled through the mixture until the debenzylation was completed (TLC control). After removal of the catalyst by filtration through Celite, the filtrate was evaporated to yield 0.18 g (quant.) of (2*R*,5*R*)-**7a** as a colourless oil. – $[\alpha]_D^{20}$ = – 5.2° (*c* = 1.3, Ethanol) [Lit.[7] $[\alpha]_D^{20}$ = – 7.6° (*c* = 3.0, Ethanol)]. – IR (film): ν/cm^{-1} = 3 382, 2 928, 2 884, 2 691, 1 456, 1 120. – ^{1}H NMR (200 MHz, $CDCl_3$): δ/ppm = 1.41–1.54 (m, 2H, 3-H, 4-H), 1.86–1.97 (m, 2H, 3-H, 4-H), 2.92 (br. s, 1H, NH), 3.25–3.47 (m, 6H, 2-H, 5-H, $2CH_2O$), 3.35 (s, 6H, $2OCH_3$). – ^{13}C NMR (75 MHz, $CDCl_3$): δ/ppm = 27.56 (C-3, C-4), 56.73, 58.74 (C-2, C-5, 2 OCH_3), 75.55 (2 CH_2O). – GC/MS (70 eV, 220 °C): *m/z* (%) = 159 (57, M^+), 113 (100), 82 (48).

$C_8H_{17}NO_2$	C 60.33	H 10.77	N 8.80	
(159.13)	C 60.62	H 10.61	N 8.95.	

(2S,5S)-**7a** *was obtained from* (2S,5S)-**6a**

$[\alpha]_D^{20}$ = + 5.0° (*c* = 1.1, Ethanol) [Lit.[7] $[\alpha]_D^{20}$ = + 7.8° (*c* = 3.0, Ethanol)]

$C_8H_{17}NO_2$	C 60.33	H 10.77	N 8.80	
(159.13)	C 60.59	H 10.92	N 8.97.	

(2R,5R)-Bis(benzyloxymethyl)pyrrolidine (**7b**) [9]

(2*R*,5*R*)-**6b** (0.09 g, 0.22 mmol) was debenzylated according to the preparation of (2*R*,5*R*)-**7a**, using 20% $Pd(OH)_2/C$ (0.02 g) as catalyst, to yield 0.06 g (90%) of (2*R*,5*R*)-**7b** as a colourless oil. – $[\alpha]_D^{25} = -2.8°$ (*c* = 1.3, $CHCl_3$) [Lit.[9] $[\alpha]_D^{25} = -3.27°$ (*c* = 1, MeOH)]. – IR (film): ν/cm^{-1} = 3 385, 2 930, 1 454, 1 122. – ^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm = 1.73–1.82 (m, 2H, 3-H, 4-H), 2.03–2.11 (m, 2H, 3-H, 4-H), 3.60–3.74 (m, 4H, $2CH_2O$), 3.77–3.89 (m, 2H, 2-H, 5-H), AB-signal (δ_A = 4.52, δ_B = 4.61, *J* = 12.0 Hz, $2OCH_2Ph$), 7.25–7.30 (m, 10H, H_{arom}). – ^{13}C NMR (75 MHz, $CDCl_3$): δ/ppm = 27.07 (C-3, C-4), 58.47 (C-2, C-5), 69.84, 73.07 ($2CH_2O$, $2OCH_2Ph$), 127.52, 127.72, 128.19, 137.65 (C_{arom}). – GC/MS (70 eV, 220 °C): *m/z* (%) = 311 (2, M^+), 190 (55), 91 (100).

$C_{20}H_{25}NO_2$	Calcd.: C 77.12	H 8.10	N 4.50
(311.19)	Found: C 77.38	H 8.27	N 4.71.

(2*S*,5*S*)-**7b** was obtained from (2*S*,5*S*)-**6b**; $[\alpha]_D^{20} = +2.9°$ (*c* = 1.1, $CHCl_3$).

$C_{20}H_{25}NO_2$	Calcd.: C 77.12	H 8.10	N 4.50
(311.19)	Found: C 77.35	H 7.95	N 4.69.

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