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TETRAHEDRON: *ASYMMETRY*

Diastereoselective synthesis of (−)-1-methyl-(3*S*,4*R*)-3,4-bis((2*S*)-*N*-(*tert*-butyloxycarbonyl)pyrrolidin-2-yl)-2-pyrrolidinone by an asymmetric Michael reaction

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Abstract

Beginning with enantiomerically pure L-proline, (−)-1-methyl-(3*S*,4*R*)-3,4-bis((2*S*)-*N*-(*tert*-butyloxycarbonyl)pyrrolidin-2-yl)-2-pyrrolidinone was prepared in diastereomerically pure form. Taking advantage of the chiral induction of the L-proline derivatives, the intermolecular Michael reaction, used to build the pyrrolidinone ring, was carried out stereoselectively.

1. Introduction

Based upon intra- and intermolecular Michael reactions, used for the preparation of carbazoles and indolocarbazoles,[1] we had synthesized 3,4-disubstituted pyrrolidin-2-one derivatives.[2] Starting with an intermolecular Michael reaction of a nitroethenyl derivative with a 2-substituted methyl acetate, subsequent reduction of the nitro group afforded a 2,3-disubstituted methyl butanoate. The following aminolysis of the butanoate yielded the aspired γ-lactam. Diastereo- and enantioselective Michael reactions are well known.[3] In most cases, the chiral information is transferred by using chiral amines, lithium amides as bases,[3a–d] chiral phase transfer catalysts,[3e–f] chiral crown ethers with complexed potassium bases,[3g] transition metal complexes, or chiral Michael donors.[3h] Our method (chiral Michael donor and chiral Michael acceptor) shows a good chiral induction when using L-proline derivatives, and yielded a stereoisomeric pure diastereomer.

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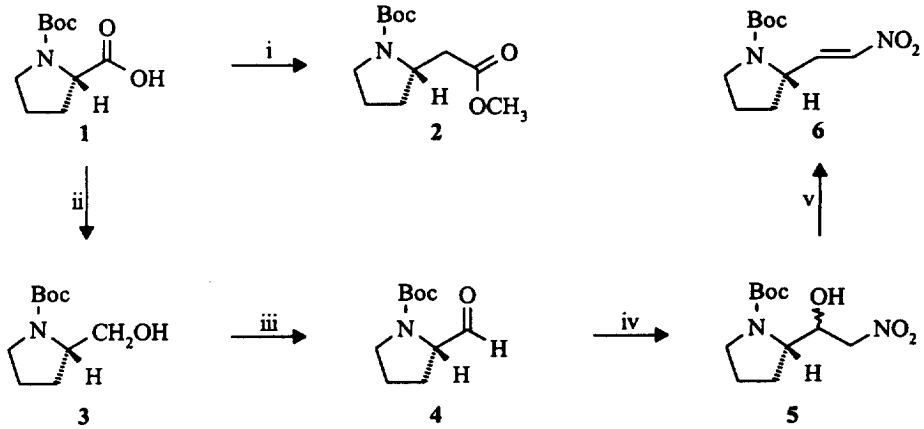
2. Results and discussion

Starting from *N*-Boc-L-proline **1**, we synthesised both the Michael donor **2** and the Michael acceptor **6**. We obtained **2** according to the procedure of Ondetti et al.[4] by an Arndt–Eistert-homologisation of **1**. According to Casal et al.[5] this homologisation proceeds with retention of the configuration of the stereocentre in the pyrrolidine ring. Methyl 2-((2*S*)-*N*-*tert*-butyloxycarbonylpyrrolidin-2-yl)acetate **2** is known[6] but has not been fully characterised.

Compound **4** was prepared from **1** by known methods.[1f] Treatment of **4** with nitromethane afforded the nitro-alcohol **5**, which was converted to the nitroalkene **6** by a modified route for the dehydration of nitro-alcohols. In a one-pot reaction, a better leaving group was introduced into **5** by using CH_3SO_2Cl followed by the β-elimination with triethylamine[7] (Scheme 1). The resulting crude mixture was chromatographed directly without any work-up because otherwise the product underwent rapid decomposition in the presence of water.



Scheme 1. (i) 1. CH_2N_2, 2. AgOBz/MeOH; (ii) $BH_3 \cdot S(CH_3)_2$; (iii) DMSO, $C_2O_2Cl_2$; (iv) CH_3NO_2, KOH; (v) 1. CH_3SO_2Cl, 2. NEt_3

The Michael reaction of **2** and **6** at −78°C with lithium diisopropylamide as a base, followed by warming of the reaction mixture to room temperature yielded the nitrobutanoate **7**. We did not detect the presence of diastereomers by thin-layer chromatography, developed in various solvent systems. Furthermore, to be sure that no mixture of diastereomers had been formed, the residue of the reaction was fractionated by column chromatography. The separated fractions were first analysed by mass spectrometry (FAB method) to locate product **7**. From those fractions containing **7**, we determined the specific rotation $[\alpha]_D^{20}$ and also analysed the ^{1}H-NMR spectra. All fractions showed the same rotation $[\alpha]_D^{20}=-79\pm2$. The ^{1}H-NMR spectra of various fractions showed no significant differences that would indicate the formation of diastereomers, even when taken at elevated temperatures (T=343, 373, 403 K). Therefore, we assume a diastereomeric excess >95%. Nevertheless, the t.l.c. detected product was completely processed in this and in all the following purification and work-up steps.

The high diastereoselectivity in this reaction can be explained by the possible transition state of the Michael reaction. Assuming that both reactants are represented by low-energy conformations similar to those shown in Fig. 1, the phenomenon of matched pairs in double diastereoselective reactions can be used to describe the effects of the steric hindrance by the substituents at the reacting centres on the course of reaction.[8] In Fig. 1 compound **2** is represented by its lithium enolate intermediate. In the transition state the two bulky pyrrolidine substituents adopt an antiperiplanar conformation, so pointing to opposite directions. Only the two small pyrrolidine 2-H atoms point directly to the reaction partner.

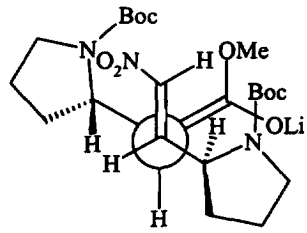
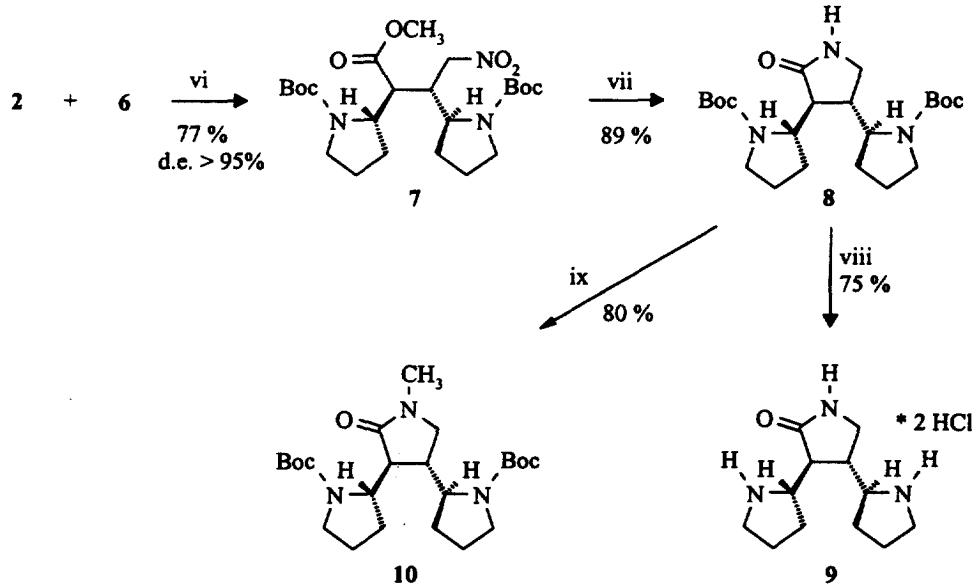


Fig. 1. Newman projection: possible transition state

This configuration of Michael donor and Michael acceptor is the only one that allows an approach of the reaction centres with a minimum of unfavourable steric interaction. This transition state already preforms the s-*trans* conformation of the two pyrrolidine substituents in compound **7**.

The formation of the lactam was accomplished by reduction of the γ-nitrobutanoate **7** with H_2/Raney-Ni and subsequent refluxing of the crude amine in toluene. Purification by column chromatography afforded the pyrrolidinone **8** (Scheme 2). The Boc-protecting groups of **8** were removed with trimethylsilyliodide (TMSI) and acetic acid; the free base **9** was converted into its hydrochloride by ethereal hydrochloric acid. The reaction of the lactam nitrogen of **8** with methyl iodide and NaH yielded 80% of the title compound **10**. Compound **10** forms uniform crystals for X-ray crystal structure analysis. For **8** and **9**, no mixtures of diastereomers could be detected, either by t.l.c. or by ^{1}H-NMR spectroscopy.



Scheme 2. (vi) LDA, THF, −78°C to room temp.; (vii) 1. Raney-Ni/H_2, 2. Δ, toluene; (viii) 1. TMSI, $CHCl_3$, 2. AcOH, 3. NaOH, 4. Et_2O, HCl; (ix) 1. NaH, 2. CH_3I

2.1. X-Ray crystal structure analysis[9]

The absolute configuration of the stereocentres in (−)-1-methyl-(3*S*,4*R*)-3,4-bis((2*S*)-*N*-(*tert*-butyloxycarbonyl)pyrrolidin-2-yl)-2-pyrrolidinone **10** was established by X-ray single crystal structure analysis. A single crystal of **10**, crystallising from ether by slow evaporation of the solvent, with the approximate size of 0.16×0.512×0.96 mm^3 was employed. The compound crystallises in the orthorhombic space group $P2_12_12_1$ with a=6.1554(1) Å, b=16.7974(3) Å and c=23.6797(5) Å;

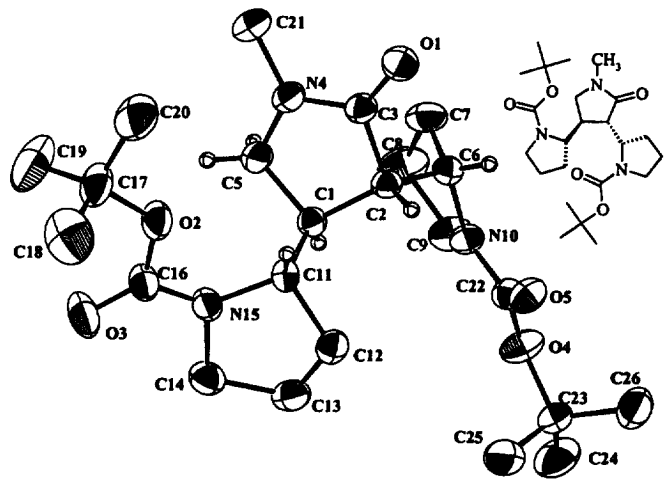


Fig. 2. X-Ray structure of (−)-1-methyl-(3*S*,4*R*)-3,4-bis((2*S*)-*N*-(*tert*-butyloxycarbonyl)pyrrolidin-2-yl)-2-pyrrolidinone **10** showing crystallographic numbering scheme

V=2448.33(8) Å^3, Z=4, D_c=1.187 g cm^{-3}, μ=0.86 mm^{-1}. The intensities were measured on an Enraf–Nonius Turbo-CAD4 diffractometer in the ω/2θ scan mode. The total 5220 (with Friedel Pairs) reflections in the range of 1.5°≤θ≤75° utilising CuKα radiation (λ=1.5418 Å) and 4622 unique reflections were used for the structure determination. The structure was solved by direct methods using SIR92[10] and refined by full matrix least squares (SHELXL-93[11]) with anisotropic displacement parameters for the non-hydrogen atoms. The positions of the hydrogen atoms were obtained from difference Fourier maps and refined isotropically. The final R1-value is 0.0435 for 4360 reflections with $I \geq 2\sigma(I)$. The absolute configuration was established using the Flack parameter [x=0.01(20)].[12] Fig. 2 shows a view (ORTEP plot, thermal ellipsoids for 40% probability[13]) of the molecule with the numbering system.

We conclude that our method, which uses two chiral parent compounds for Michael reactions with their stereogenic centres near the reacting centre, is applicable for the introduction of two new stereogenic centres in a nitrobutanoate. These two new chiral centres preform the stereogenic information for the 3- and 4-position of the desired γ-lactam. Good overall yields and a high diastereoselective excess in the main step are promising features of this reaction. We now are exploring further applications for this highly diastereoselective Michael reaction.

3. Experimental

3.1. General

Melting points were recorded on a Reichert Thermovar 300419 microscope heating stage and are not corrected. Proton nuclear magnetic resonance spectra were recorded on a Bruker ARX400 (400 MHz), a Bruker AC250 (250 MHz), or a Varian EM 390 (90 MHz) spectrometer. All chemical shifts are quoted on the δ-scale. The following abbreviations were used to explain multiplicities: s, singlet; d, doublet; dd, double doublet; m, multiplet; br., broad. Mass spectra were recorded on a Varian MAT 112 S, 70 eV using electron impact ionisation (EI) or on a Finnigan MAT 95 for field desorption (FD) or atomic bombardment (FAB) as stated. Optical rotations were measured on a Perkin–Elmer 241 MC polarimeter. FT-IR spectroscopy was performed on a Nicolet 510 FT-IR spectrometer. Microanalyses were performed

by Analytisches Lab. Univ. Regensburg. Thin layer chromatography (t.l.c.) was carried out on Al-sheets coated with $60F_{245}$ silica. Compounds were detected using a spray of 3% w/v vanillin in 96% ethanol and 5% w/v H_2SO_4 in 96% ethanol. Column chromatography was carried out using Merck 60 (70–230 mesh ASTM) silica. Solvents and commercially available reagents were dried and purified before use according to standard procedures. All reactions were carried out under dried N_2 in flame- or oven-dried vessels.

3.2. *Methyl 2-((2S)-*N*-tert-butyloxycarbonylpyrrolidin-2-yl)acetate* **2**

tert-Butyloxycarbonyl-L-proline **1** (5.00 g, 23.2 mmol) was dissolved in dry diethyl ether (50 ml) and triethylamine (3.24 ml, 23.2 mmol). The solution was cooled and stirred at −5°C, and ethyl chloroformate (2.27 ml, 23.2 mmol) was added. After 5 min, the triethylamine hydrochloride precipitate was filtered off, and an ether solution of diazomethane (prepared from 6.50 g (63.1 mmol) *N*-methyl-*N*-nitrosourea) was added to the filtrate. The reaction mixture was stirred for 16 h at 5–20°C, the solvent was removed *in vacuo*, the oily, yellow residue was dissolved in ethyl acetate (30 ml) and washed with saturated sodium hydrogen carbonate solution (20 ml) and water (20 ml). The organic layer was dried over Na_2SO_4 and concentrated to dryness *in vacuo*. The crude diazomethyl ketone (3.75 g) was dissolved in dry methanol (16 ml), and 10 drops of a solution of silver benzoate (0.45 g) in dry triethylamine (4.20 ml) were added with stirring. Evolution of N_2 and an increase of temperature were observed. The mixture was stirred at room temperature for 10 h, treated with activated charcoal and concentrated to dryness *in vacuo*. The black, oily residue was dissolved in ethyl acetate and washed until neutral. After drying over Na_2SO_4, the solvent was removed *in vacuo* and the residue was purified by column chromatography ($CHCl_3$) to yield the methyl ester **2** as a colourless oil (2.46 g, 10.1 mmol, 44%); $[\alpha]_D^{20}=-38.8$ (c=16, MeOH); IR (film): ν (cm^{-1})=2977, 2880 (CH); 1740, 1697 (CO); ^{1}H-NMR ($CDCl_3$, 90 MHz): δ (ppm)=3.67 (s; 3H, $COOCH_3$), 3.27–3.43 (m; 2H, N–CH_2), 2.75–2.97 (m; 1H, N–CH), 1.71–2.56 (m; 6H), 1.47 (s; 9H, $C(CH_3)_3$); EI-MS: m/z (%)=243 (4) [$M^{+\cdot}$], 187 (9) [$M-C_4H_8]^{+\cdot}$, 170 (8) [187−OH]$^+$, 142 (35) [$M-C(CH_3)_3$–O–C=O]$^+$, 70 (100) [$C_4H_8N]^+$; anal. calcd for $C_{12}H_{21}NO_4$ (243.30): C 59.24; H 8.70; N 5.76. Found: C 58.45; H 8.68; N 5.70.

3.3. *(2S)-*N*-(tert-Butyloxycarbonyl)-2-(2-nitro-hydroxyethyl)pyrrolidine* **5**

Compound **4** (0.50 g, 2.51 mmol) was dissolved in freshly distilled nitromethane (1.50 ml, 28.1 mmol) and 5 drops of a 3 N solution of KOH in methanol were added. The mixture was stirred for 1 h at room temperature, 1 drop of conc. H_2SO_4 was added and the resulting mixture was stirred for another hour until pH 2–3 was reached. Subsequently, the mixture was transferred directly to a chromatography column ($CHCl_3$) without any previous work-up and the product was separated. Removing the solvent under reduced pressure gave a colourless oil, which later crystallised at the oil-pump. The nitro alcohol **5** (0.63 g, 2.42 mmol, 96%) was isolated as colourless needles melting between 57 and 94°C (mixture of diastereomers); IR (film): ν (cm^{-1})=3404 (OH); 2979, 2934, 2890 (CH); 1671 (CO); 1557 (NO); ^{1}H-NMR ($CDCl_3$, 90 MHz): δ (ppm)=4.35–4.53 (m; 2H, CH_2–NO_2), 3.89–4.09 (m; 2H), 3.13–3.60 (m; 2H), 1.76–2.44 (m; 4H), 1.49 (s; 9H, $C(CH_3)_3$); EI-MS: m/z (%)=200 (0.1) [$M-CH_2NO_2]^+$, 187 (8) [$M-C_4H_9O]^+$, 170 (26) [$M-CH(OH)-CH_2NO_2]^+$, 70 (100) [$C_4H_8N]^+$; anal. calcd for $C_{11}H_{20}N_2O_5$ (260.29): C 50.76; H 7.74; N 10.76. Found: C 50.69; H 7.64; N 10.68.

3.4. (2S)-N-(tert-Butyloxycarbonyl)-2-(2-(E)-nitroethenyl)pyrrolidine 6

Compound **5** (1.00 g, 3.84 mmol) was dissolved in dry methylene chloride (2 ml) at 0°C, and methane sulfonylchloride (0.44 ml, 1.73 mmol) was added dropwise over 15 min. Dry triethylamine (1.00 ml, 6.92 mmol) was then added dropwise, and the reaction mixture was stirred for 15 min at 0°C. Without any previous work-up the mixture was immediately chromatographed ($CHCl_3$). The solvent was evaporated under reduced pressure and the resulting yellow oil crystallised after several days in the refrigerator, yielding the nitroethene **6** (0.88 g, 3.63 mmol, 95%) as yellow crystals; m.p. 40°C; $[\alpha]_D^{20}=-81.7$ (c=8, MeOH); IR (film): ν (cm^{-1})=3108, 2979, 2934, 2882 (CH); 1694 (CO); 1526 (NO); ^{1}H-NMR ($CDCl_3$, 250 MHz): δ (ppm)=7.13 (dd; J_1=13.2 Hz, J_2=6.0 Hz, 1H, C*H*=CH–NO_2), 6.97 (d; J=13.2 Hz, 1H, CH=C*H*–NO_2), 4.45–4.57 (m; 1H, N–CH), 3.44 (br. s; 2H, N–CH_2), 2.17 (m; 1H), 1.82–1.99 (m; 3H), 1.44 (s; 9H, $C(CH_3)_3$); EI-MS: m/z (%)=242 (1) [$M^{+\cdot}$], 196 (0.2) [$M-NO_2$]$^+$, 186 (8) [$M-C_4H_8$]$^{+\cdot}$, 169 (10) [$M-C_4H_9O$]$^+$, 70 (11) [C_4H_8N]$^+$, 57 (100) [C_4H_9]$^+$; anal. calcd for $C_{11}H_{18}N_2O_4$ (242.28): C 54.53; H 7.49; N 11.56. Found: C 54.53; H 7.33; N 11.61.

3.5. (−)-(2S,3R)-Methyl 4-nitro-2,3-bis((2S)-N-(tert-butyloxycarbonyl)pyrrolidin-2-yl)butanoate 7

To a solution of dry diisopropylamide (3.80 ml, 26.0 mmol) in dry THF (9.2 ml) in a three-necked flask, equipped with a deep-temperature thermometer and a septum, was added *n*-BuLi (10.2 ml, 16.2 mmol) at −78°C within 30 min. After stirring at 0°C for 30 min and recooling to −78°C, **2** (3.00 g, 2.3 mmol), dissolved in dry THF (40 ml), was added by a syringe within 30 min. The resulting mixture was stirred for 30 min at −78°C and subsequently **6** (3.60 g, 14.9 mmol), dissolved in dry THF (30 ml), was added by a syringe. The resulting mixture was stirred overnight and allowed to warm to room temperature. Standard NH_4Cl solution (100 ml) was added in one portion. The organic layer was separated and the aqueous layer was extracted with diethyl ether (500 ml). The combined organic layers were dried over Na_2SO_4, and the solvent was evaporated *in vacuo*. Purification of the yellow residue by column chromatography (Et_2O:hexane=1:1) and recrystallisation from pentane yielded the pure nitrobutanoate **7** as a single diastereomer (4.61 g, 9.49 mmol, 77%). Colourless powder; m.p. 52–54°C; $[\alpha]_D^{20}=-79.0$ (c=10.2, MeOH); IR (KBr): ν (cm^{-1})=2977, 2889 (CH); 1737, 1698 (CO); 1553 (NO); ^{1}H-NMR ($C_2D_2Cl_4$, 400 MHz, 403 K): δ (ppm)=4.58–4.94 (m; 2H), 3.99–4.21 (m; 2H), 3.62–3.66 (m; 3H), 3.42–3.48 (m; 2H), 3.09–3.29 (m; 3H), 2.79–2.82 (m; 1H), 1.70–2.04 (m; 8H), 1.43–1.46 (m; 18H); FD-MS: m/z=486 [$M^{+\cdot}$]; EI-MS: m/z (%)=485 (0.1) [$M^{+\cdot}$], 439 (0.2) [$M-NO_2$]$^+$, 356 (1) [$M-C_4H_9O$]$^+$, 170 (26) [(C_4H_7N)–Boc]$^+$, 70 (77) [C_4H_8N]$^+$, 57 (100) [C_4H_9]$^+$; anal. calcd for $C_{23}H_{39}N_3O_8$ (485.58): C 56.89; H 8.10; N 8.65. Found C 56.71; H 7.77; N 8.63.

3.6. (−)-(3S,4R)-3,4-Bis((2S)-N-(tert-butyloxycarbonyl)pyrrolidin-2-yl)-2-pyrrolidinone 8

A solution of **7** (4.50 g, 9.27 mmol) in dry diethyl ether (25 ml) and dry ethanol (25 ml) was hydrogenated over Raney-Ni (10 g) with 12 bar H_2. After 48 h the autoclave was flushed with nitrogen, the reaction mixture was filtered through Celite® and the Celite® pad was washed with warm ethanol. The solvent was evaporated under reduced pressure, the residue dissolved in toluene (75 ml) and the mixture refluxed for 2 h. The toluene was removed *in vacuo* and the residue purified by column chromatography (CH_2Cl_2:ethyl acetate:methanol=3:3:0.5) affording the pyrrolidinone **8** (3.48 g, 8.22 mmol, 89%) as a colourless, amorphous powder; m.p. 186–188.5°C; $[\alpha]_D^{20}=-90.0$ (c=0.33, MeOH); IR (KBr): ν (cm^{-1})=3397 (NH); 2975 (CH); 1694 (CO); ^{1}H-NMR ($C_2D_2Cl_4$, 400 MHz, 373 K): δ (ppm)=5.10–5.37 (m; 1H), 3.75–4.56 (m; 2H), 3.07–3.68 (m; 6H), 2.23–3.07 (m; 1H), 1.52–2.07 (m;

7H), 1.33–1.49 (m; 20 H); FD-MS: m/z=423 [$M^{+\cdot}$]; anal. calcd for $C_{22}H_{37}N_3O_5$ (423.55): C 62.39; H 8.80; N 9.92. Found C 62.08; H 8.59; N 9.79.

3.7. (+)-(3S,4R)-3,4-Bis((2S)-pyrrolidin-2-yl)-2-pyrrolidinonedihydrochloride 9

A solution of **8** (0.10 g, 0.22 mmol) in dry chloroform (2.2 ml) was cooled to 0°C, and trimethylsilyl iodide (TMSI) (0.17 ml) was added dropwise by a syringe. After 10 min stirring at room temperature methanol (1.2 ml) was added in one portion. After 5 min all volatile components were removed *in vacuo* and the residue was dissolved in diethyl ether (4 ml) and acetic acid (4 ml, 30%). The aqueous layer was separated, washed with diethyl ether (2×5 ml) and evaporated to dryness *in vacuo*. The brown residue was stirred with a mixture of 6 N NaOH (10 ml) and methylene chloride (10 ml) for 12 h. The organic layer was separated, dried over Na_2SO_4 and concentrated to dryness. The white residue was dissolved in diethyl ether (3 ml) and a standard ethereal solution of HCl (2 ml) was added dropwise. The white precipitate was filtered off and recrystallised from methanol, affording **9**-hydrochloride (50.3 mg, 0.17 mmol, 75%) as colourless crystals; m.p.: 236–237°C (decomp.); $[\alpha]_D^{20}$=+44.3 (c=0.79, MeOH); IR (KBr): ν (cm^{-1})=3537, 2761 (NH); 2942 (CH); 1700 (CO); ^{1}H-NMR (CD_3OD, 250 MHz): δ (ppm)=3.64–3.80 (m; 3H), 3.30–3.42 (m; 5H), 2.74–2.85 (m; 1H), 2.60–2.66 (m; 1H), 2.28–2.45 (m; 2H), 1.66–2.20 (m; 6H); FAB-MS: m/z=224 [M+H]$^{+\cdot}$; anal. calcd for $C_{12}H_{23}Cl_2N_3O \cdot 0.5H_2O$ (305.25): C 47.22; H 7.90; N 13.77; Found: C 47.23; H 7.20; N 13.79.

3.8. (−)-1-Methyl-(3S,4R)-3,4-bis((2S)-N-(tert-butyloxycarbonyl)pyrrolidin-2-yl)-2-pyrrolidinone 10

Compound **8** (0.30 g, 0.71 mmol) was dissolved in dry THF (30 ml), NaH (27.5 mg, 0.92 mmol, 80% suspension in oil) was added, and the mixture was refluxed for 1 h. After cooling to room temperature methyl iodide (8.80 ml, 0.14 mol) was added, and the mixture was refluxed for 1 h. After cooling, water (5 ml) was added carefully. The organic layer was separated and the aqueous layer was extracted with diethyl ether (50 ml). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The resulting brown residue was purified by column chromatography (ethyl acetate:hexane=1:1) and the product was recrystallised from diethyl ether, yielding the *N*-methylpyrrolidinone **10** (0.25 g, 0.57 mmol, 80%) as colourless, cubic crystals; m.p. 143–145°C; $[\alpha]_D^{20}$=−113.4 (c=1.7, MeOH); IR (KBr): ν (cm^{-1})=2975, 2934, 2884 (CH); 1690 (CO); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm)=3.70–4.30 (m; 4H), 3.07–3.70 (m; 7H), 2.83 (s; 3H, N–CH_3), 1.65–2.33 (m; 10H), 1.49 (s; 15H); FD-MS: m/z=437 [$M^{+\cdot}$]; anal. calcd for $C_{23}H_{39}N_3O_5$ (437.58): C 63.13; H 8.98; N 9.60. Found: C 63.17; H 8.97; N 9.42.

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