DOI: 10.1002/ejoc.201100404

A Novel Rearrangement of Cyclic Glutamine Derivatives: Ring Contraction in 3,6-Diamino-2,3,4,5-tetrahydropyridin-2-ones to Yield 5-Iminoproline Amides

Vladimir N. Belov,*[a][‡] Viktor V. Sokolov,[a][‡‡] Boris D. Zlatopolskiy,[b] and Armin de Meijere*[a]

Dedicated to Professor Oleg Nefedov on the occasion of his 80th birthday

Keywords: Rearrangement / Amino acids / Nitrogen heterocycles / Cyclization

A new rearrangement of the cyclic L-glutamine derivative (*S*)-6-carbamoylamino-3-(methylamino)-2,3,4,5-tetrahydropyridin-2-one (**2**) and its descarbamoyl analogue **10**-H was found to yield enantiomerically pure 5-carbamoylimino-1-methyl-L-proline amide (**12**-$CONH_2$) and its descarbamoyl analogue **12**-H, respectively. Cyclic amidines **2** and **10**-H were generated from the amide N^2-ZGlnOEt **3** in seven and six steps, respectively. Deprotection of (*S*)-6-amino-3-[(*N*-benzyloxycarbonyl-*N*-methyl)amino]-2,3,4,5-tetrahydropyridin-2-one (**8**) led directly to 5-iminoproline amide **12**-H (via **10**-H and the bicyclic orthoamidine **11**-H) in 66% overall yield from **3**. Carbamoylation of **8** with ZNCO (Z = $PhCH_2OCO$) followed by hydrolytic removal of both Z groups gave 5-(carbamoylimino)proline amide **12**-$CONH_2$ (via **2** and orthoamidine **11**-$CONH_2$) in 70% overall yield from **3**.

Introduction

The total synthesis of the new naturally occurring antibiotic TAN-1057A/B[1] and various structural analogues have been the subject of numerous investigations.[2] In the course of a number of structure–activity relationship studies,[2d,2j–2m] several analogues of the TAN-1057A/B heterocycle **1** have also been prepared. For example, replacement of N-3 in tetrahydropyrimidinone fragment **1** with a carbon atom has recently been reported (Figure 1).[2f] Another interesting option was conceived to be substitution of the other nitrogen atom (N-1) in fragment **1** with a CH_2 group. This replacement would convert the acylated guanidine moiety in **1** into an acylated amidine moiety. The required tetrahydropyridinone derivative **2** was anticipated to be susceptible to hydrolysis, as it contains an amidine fragment bearing an *N*-acyl and an *N*′-carbamoyl group, and its central carbon atom would be much more electron deficient than that of the *N*,*N*′-diacylated guanidine group in compound **1**. However, a very similar type of functionality had previously been described,[2f,3] and acylated amidines were not reported to be highly susceptible to hydrolysis. Replacement of N-1 in heterocycle **1** with a carbon atom would be advantageous, as it would convert the 2,3-diaminopropionic acid fragment in **2** into a configurationally more stable glutamine residue.

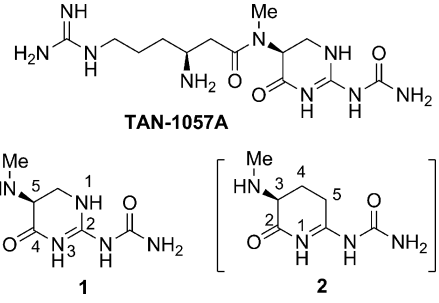


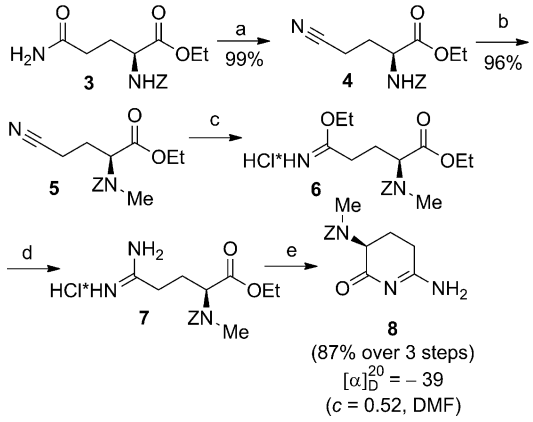
Figure 1. N^1-Deaza analogue **2** of heterocycle **1**, the key fragment of the biologically most potent A-diastereomer of the natural antibiotic TAN-1057.

Results and Discussion

The best starting material for compound **2** was envisaged to be L-glutamine. A literature search indicated that L-glutamine should easily be transformable into tetrahydropyridinone derivative **2** with the same configuration at the

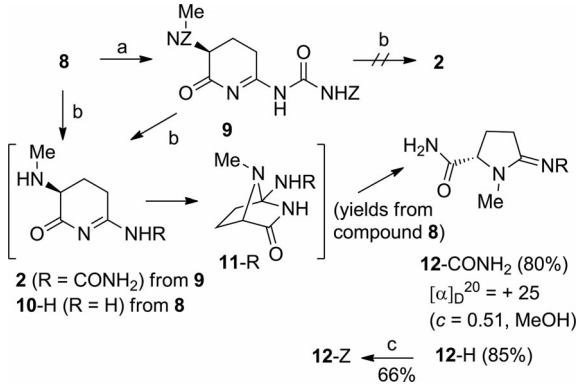
[a] Institut für Organische und Biomolekulare Chemie der Georg-August-Universität Göttingen,
Tammannstrasse 2, 37077 Göttingen, Germany
Fax: +49-551-393231
E-mail: ameijer1@gwdg.de
[b] Klinik für Nuklearmedizin, Aachen University, RWTH, Pauwelsstr. 30, 52074 Aachen, Germany
[‡] Current address: Facility für Synthetische Chemie, Max-Planck-Institut für Biophysikalische Chemie, Am Fassberg 11, 37077 Göttingen, Germany
Fax: +49-551 2012505
E-mail: vbelov@gwdg.de
[‡‡]Permanent address: Department of Chemistry, Saint Petersburg State University, Universitetskii pr. 26, 198054 Saint Petersburg, Russia

stereogenic center as in the biologically most potent A-diastereomer of TAN-1057. Indeed, cyclic amidines with one acylated nitrogen incorporated into a five- or six-membered ring are easily available from ethyl 3-cyanopropionate or 4-cyanobutyrate, respectively, by a three-step procedure starting with the transformation of the nitrile into an imino ester[4] followed by aminolysis and spontaneous cyclization of the resulting amidine to yield 2-amino-1-pyrrolin-5-one or 6-amino-2,3,4,5-tetrahydropyridin-2-one.[5] Tetrahydropyridinone derivative **2** should thus be accessible by performing an analogous transformation with Z-protected ethyl 2-amino-4-cyanobutyrate (**5**, Z = $PhCH_2OCO$). To obtain ester **5**, N^2-Z-L-glutamine[6] was first converted into N^2-ZGlnOEt[7] (**3**, Scheme 1), and then the amide moiety in amido ester **3** was dehydrated under very mild conditions, that is, by treatment with trifluoroacetic anhydride/pyridine in dichloromethane.[8] The newly installed nitrile function in **4** played an important role in the subsequent transformations for two reasons: Compound **4** could be selectively methylated at N-2 without competitive N^{ω}-methylation.[9] After that, the nitrile group in resulting **5** cleanly underwent the Pinner transformation, that is, conversion into imino ester **6** by treatment with hydrogen chloride in ether in the presence of ethanol (Scheme 1). To keep the Z protecting group intact, this reaction was carried out at –5 to –10 °C. When run at the temperature of an ice bath,[4] benzyl chloride, formed by cleavage of the Z protective group, could be extracted with diethyl ether from salt **7** to the extent of ca. 10 mol-%.



Scheme 1. Synthesis of Z-protected (*S*)-6-amino-3-(methylamino)-2,3,4,5-tetrahydropyridin-2-one (**8**) as a potential key intermediate en route to the tetrahydropyridinone derivative **2** (Z = $C_6H_5CH_2OCO$). Reagents and conditions: (a) $(CF_3CO)_2O$, pyridine, CH_2Cl_2, 0 °C to r.t.; (b) MeI, Ag_2O, DMF, 0 °C to r.t.; (c) gaseous HCl, EtOH, ether, –10 to –5 °C; (d) 10% NH_3 in EtOH; (e) 20% aq. NaOH.

Upon treatment with a slight excess amount of dry ammonia in anhydrous ethanol at room temperature, imino ester **6** was smoothly transformed into amidine **7**. Then ethanol was evaporated, and aqueous NaOH was added to the oily residue with cooling. The solution was adjusted to pH 12–13. The thick precipitate that was immediately formed turned out to be the desired compound **8**. Carbamoylation of the exocyclic nitrogen atom of the ring-incorporated amidine group in compound **8** was achieved under anhydrous conditions with the very reactive benzyloxycarbonyl isocyanate[10] (Z-isocyanate, Scheme 2). Subsequent hydrogenolytic removal of both Z groups in resulting **9** was expected to afford required **2** with a secondary amino group in the 3-position. Indeed, the isolated product had the required molecular mass as proved by electron impact ionization (EI) mass spectrometry and showed seven signals in the ^{13}C NMR spectrum. Thus, the target seemed to be achieved in seven steps with a high overall yield (66%). However, in the ^1H NMR spectrum (in $[D_6]$DMSO), the signals of *all* NH protons are *singlets* with chemical shifts >6 ppm, so that none of them could be attributed to the aliphatic amino group. Moreover, no fragmentation with an elimination of the methylamino residue was registered in the EI mass spectrum, although such an elimination under electron impact ionization is well documented for tetrahydropyrimidinone derivative **1** and its analogues.[1,2] Yet, the alternative structure **12**-$CONH_2$ fits all the observed spectroscopic data. For example, in the 2D NOESY spectrum, the cross-peaks indicate that four amide protons form two pairs. The signal of a CH proton has cross-peaks with the signals of two amide protons belonging to one pair. As expected, the rearranged compound **12**-$CONH_2$ could not be acetylated with AcOH in the presence of *N*-[3-(dimethylamino)propyl]-*N*′-ethylcarbodiimide and 4-(dimethylamino)pyridine (10%) (EDC/DMAP) at room temperature in dimethylformamide.[11]



Scheme 2. Ring contraction in (*S*)-6-amino-3-(methylamino)-2,3,4,5-tetrahydropyridin-2-ones **2** and **10**-H. Reagents and conditions: (a) ZNCO, DMF, 0 °C to r.t.; (b) H_2 (1 atm), Pd/C (10% Pd, oxidized form), DMF; (c) ZOC_6F_5, *i*Pr_2NEt, DMF, 55 °C, 12 h.

The formation of compound **12**-$CONH_2$ can be rationalized by assuming that the initially formed 3-methylaminotetrahydropyridinone derivative **2** undergoes intramolecular nucleophilic addition onto the endocyclic imino group to form the rather strained 1-amino-2,7-diazabicyclo[2.2.1]-heptan-3-one derivative **11**-$CONH_2$. The bicyclic intermediate **11**-$CONH_2$ with its orthoamidine moiety cycloreverts with the acylamino group acting as the better nucleofuge and forms the stable 5-carbamoylimino-1-methylproline amide (**12**-$CONH_2$) with a *new* amidine fragment incorpo-

rated into a five-membered ring. This new amidine fragment is deprived of the activating acyl group in precursor **2**.

Interestingly, when compound **8** was directly subjected to hydrogenolysis without carbamoylation, the same type of rearrangement also took place (**8** → **10**-H → **11**-H → **12**-H in Scheme 2). In this case, along with the spectroscopic evidence, chemical proof of the new rearrangement was provided by conversion of amidine **12**-H into the corresponding *N*-benzyloxycarbonyl derivative **12**-Z by using *O*-benzyloxycarbonylpentafluorophenol (ZOC_6F_5), and it was shown that compounds **12**-Z and **8** are not identical.

A sample of compound **12**-$CONH_2$ was analyzed on a chiral HPLC column with the teicoplanin-modified stationary phase (Chirobiotic T) in polar solvent mode optimized for the separation of amino acids (see the Experimental Section for details). This column under the given conditions reliably separates enantiomers of all natural amino acids and many of their derivatives. Only one peak with t_R = 8.1 min (area 92%) and an impurity with t_R = 2.8 min (peak area 8%) was observed. These results suggest that most likely the recrystallized sample of compound **12**-$CONH_2$ is a single enantiomer [because under the given separation conditions, the differences in retention times of the (*R*)- and (*S*)-amino acids, e.g., L- and D-pyroglutamic acids, are expected to be 1–3 min].

The scope and limitations of this new rearrangement were briefly investigated. When tetrahydropyridinone derivatives of type **9** did not contain a 3-(*N*-methylamino) group but a 3-amino group, the rearrangement was also observed, but in this case the transformation was not so clean and high yielding. When N^{α}-methylasparagine derivatives were used, the corresponding azetidine derivatives could not be isolated, but rather complex mixtures of oligomers and polymers were obtained.

Conclusion

Thus, a novel high-yielding (66–70%) route to 5-imino-1-methylproline amides **12**-$CONH_2$ and **12**-H in seven and six steps, respectively, from enantiomerically pure N^2-benzyloxycarbonyl-L-glutamine ethyl ester (**3**) is reported. Compounds **12**-$CONH_2$ and **12**-H may have interesting biological activities, as **12**-H is the amide of (*S*)-5-imino-1-methylproline, which was isolated from a highly bioactive extract of the Caribbean sponge *Cliona tenuis*.[12] The latter as well as its methyl ester have previously been prepared in five- and six-step syntheses in 42% overall yield.[12] Two 2-iminopyrrolidinecarboxylic acid derivatives have exhibited antibacterial activities,[13] and a series of substituted 2-iminopyrrolidines have been shown to be potent and selective inhibitors of human inducible nitric oxide synthase.[14]

Experimental Section

General: NMR spectra were recorded with Bruker AM 250 (250 MHz for ^{1}H and 62.9 MHz for ^{13}C) and Varian Mercury-300 (300.5 MHz for ^{1}H) spectrometers. All NMR spectra are referenced to tetramethylsilane as an internal standard (δ = 0 ppm) using the signals of the residual protons of $CHCl_3$ (δ = 7.26 ppm) in $CDCl_3$ or [D_5]DMSO (δ =2.50 ppm) in [D_6]DMSO. Multiplicities of signals are described as follows: s = singlet, br. s = broad singlet, d = doublet, m = multiplet, m_c = centrosymmetrical multiplet. EI-MS were recorded with a Finnigan MAT 95 at 70 eV and ESI-MS were recorded with a Finnigan LCQ. Elemental analyses were performed in the Mikroanalytisches Laboratorium des Instituts für Organische und Biomolekulare Chemie. Reactions were carried out under an atmosphere of argon with magnetic stirring in Schlenk flasks equipped with septa or reflux condensers with bubble counters using a standard manifold with vacuum and argon lines. The purity of the products was checked by TLC on Merck ready-to-use plates with silica gel 60 (F_{254}). Column chromatography was performed with Merck silica gel, grade 60, 0.06–0.20 mm.

Ethyl (*S*)-2-[(*N*-Benzyloxycarbonyl-*N*-methyl)amino]-4-cyanobutanoate (5): Compound **5** was synthesized from ethyl (*S*)-2-(benzyloxycarbonylamino)-4-cyanobutanoate (**4**)[7] according to the previously published general method.[9] To a mixture of compound **4** (21.4 g, 73.8 mmol) and Ag_2O (65 g, 0.28 mol) in anhydrous DMF (200 mL) was added MeI (35 mL, 80 g, 0.56 mol) dropwise at +5 to 10 °C (external cooling with water was applied). The reaction mixture was stirred overnight at room temperature and then filtered through Celite. The filter cake was washed with CH_2Cl_2 (1 L). The combined organic solutions were washed with sat. aq. $Na_2S_2O_3$ (3 × 200 mL) and then with water (8 × 300 mL). After drying of the organic solutions over $MgSO_4$, the solvent was evaporated under reduced pressure, and the residual oil was kept in vacuo (0.1 Torr) until its weight became constant (21.5 g; corresponds to 96% yield). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.17–1.28 (m, 3 H, CH_3), 2.07–2.20 (m, 1 H, 3-H), 2.31–2.46 (m, 3 H, 3-H, 4-H), 2.92 (s, 3 H, MeN), 4.07–4.24 (m, 2 H, CH_2O), 4.53–4.67 (m, 1 H, 2-H), 5.17 (s, 2 H, CH_2O), 7.26–7.36 (m, 5 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, signals of the major amide rotamer are marked*): δ = 14.1 (C-4), 14.4 (CH_3), 24.9* (C-3), 32.2*/32.6 (MeN), 58.4/58.8* (CH_2O), 61.7 (CHN), 67.7*/67.8 (CH_2O), 118.8 (CN), 127.7, 128.1, 128.5 (CH), 136.2 (C), 156.8 (CONH), 169.8 (COO) ppm.

(*S*)-6-Amino-3-[(*N*-benzyloxycarbonyl-*N*-methyl)amino]-2,3,4,5-tetrahydropyridin-2-one (8): To a solution of compound **5** (19 g, 62 mmol) in anhydrous ether (150 mL) was added anhydrous EtOH (5 mL), and the solution was saturated with dry HCl while stirring at –10 °C (cooling with an ice/NaCl mixture). The reaction mixture was kept at –5 to –10 °C overnight. Volatile materials were evaporated in vacuo at 0 °C and then at room temperature. The glassy residue was washed with anhydrous ether (2 × 50 mL; with decantation) and kept under reduced pressure (0.5 Torr) for 3 h. The residue (compound **6**) was dissolved in anhydrous EtOH (70 mL), and a 10% solution of NH_3 in EtOH was added, until the pH value of a sample of the reaction mixture diluted with water became 8–9. The reaction mixture was kept at room temperature for 22 h, the ethanol was evaporated in vacuo, and the residue (compound **7**) was dissolved in cold water (50 mL). The solution was made basic (pH 12–13) with 20% aq. NaOH added with stirring at 0 °C. A colorless voluminous precipitate was formed almost immediately. It was removed by filtration, washed with cold water, and dried to give 15.0 g (87%) of the title compound with m.p. 206–208 °C. An analytical sample (1.9 g) was recrystallized from EtOH (150 mL) and dried in vacuo; m.p. 212 °C. $[a]_D^{20}$ = –39 (*c* = 0.52, DMF). R_f = 0.27 (CH_2Cl_2/MeOH, 10:1). ^{1}H NMR (250 MHz, [D_6]DMSO, signals of the major amide rotamer are marked*): δ = 1.85 (m_c, 1 H, 4-H), 2.03 (m_c, 1 H, 4-H), 2.60 (m_c, 1 H, 5-H), 2.68 (m_c, 1 H, 5-H), 2.70/2.72* (2 s, Σ 3 H, NMe), 4.48 (m_c, 1 H, 3-H), 5.04 (A

part of AB system, J_{AB} = 12.7 Hz, CHHO), 5.08 (B part of AB system, J_{AB} = 12.7 Hz, CHHO), 5.09 (s, Σ 2 H, CH_2O), 7.32–7.38 (m, 5 H), 8.11 (br. s, 2 H, NH_2) ppm. ^{13}C NMR (62.9 MHz, [D_6]-DMSO, signals of the major amide rotamer are marked*): δ = 23.3/23.90* (CH_2), 27.3 (CH_2), 31.1/31.7* (Me), 57.1 (CH), 66.4 (CH_2O), 127.4, 127.7, 127.8, 128.0, 128.5, 128.6 (CH), 137.2 (C), 156.2 (OCON), 174.2 (C-2/6), 177.6 (C-6/2) ppm. MS (EI, 70 eV): *m/z* (%) = 275 (24) $[M]^{+\cdot}$, 231 (4), 184 (5), 156 (9), 140 (12), 112 (18), 91 (100), 83 (20), 65 (8). $C_{14}H_{17}N_3O_3$ (275.3): calcd. C 61.08, H 6.22, N 15.26; found C 60.81, H 6.34, N 15.41.

5-Carbamoylimino-1-methyl-L-proline Amide (12-CONH$_2$): To a suspension of **8** (1.6 g, 5.8 mmol) in anhydrous DMF (30 mL) was added ZNCO (1.06 g, 6.00 mmol) dropwise at room temperature. The course of the reaction was monitored by TLC on SiO_2 (CH_2Cl_2/MeOH, 10:1). Compound **9** has a higher R_f value than compound **8**. If the spot of the starting material was still detected at 254 nm, a few more drops of ZNCO were added. When the reaction was complete, 10% Pd/C (200 mg, oxidized form, VWR) was added, and the suspension was vigorously stirred for 2.5 h under an atmosphere of hydrogen. TLC indicated that compound **9** had been consumed, and a single new UV-active spot of a more polar compound with R_f = 0.19 was observed (CH_2Cl_2/MeOH, 4:1). The reaction mixture was filtered through Celite; the filter cake was washed with anhydrous DMF (10 mL). The solvent was evaporated in vacuo, and the residue was taken up in cold anhydrous ethanol. A solid colorless substance was filtered off, washed with a small amount each of cold ethanol and ether, then dried. Yield: 0.86 g (80%), m.p. 159–160 °C. $[a]_D^{20}$ = +25 (*c* = 0.51, MeOH). RP-HPLC [Gemini column, 5 µ C18, 110 Å, 4.6 × 250 mm with precolumn ("Phenomenex"); gradient: 0–4% MeOH (0–6 min), 4–90% MeOH (6–20 min), 90% MeOH (23–26 min); flow rate: 1 mL/min; detection at 220 nm, inj. vol.: 5 µL, probe conc.: 3 mg/mL, H_2O]: t_R = 4.5 min (peak area 95%). Chiral HPLC [Chirobiotic T column, 5 µ, 4.6 × 250 mm ("ISCO"); eluent: 10% aq. EtOH; flow rate: 1.7 mL/min; detection at 220 nm, inj. vol.: 10 µL, probe conc.: 1 mg/mL, H_2O]: t_R = 8.1 min (peak area 92%; one additional peak with t_R = 2.8 min). ^1H NMR (250 MHz, [D_6]DMSO): δ = 1.82 (m_c, 1 H, 3-H), 2.14 (m_c, 1 H, 3-H), 2.66–2.81 (m, 4-H), 2.73 (s, NMe, Σ 5 H), 3.98 (dd, *J* = 8.8, 3.9 Hz, 1 H, 2-H), 5.98 (br. s, 1 H, $NCONH_2$), 6.20 (br. s, 1 H, $NCONH_2$), 7.21 (s, 1 H, $CONH_2$), 7.64 (s, 1 H, $CONH_2$) ppm. ^{13}C NMR (62.9 MHz, [D_6]DMSO): δ = 25.1 (CH_2), 29.1 (CH_2), 30.4 (CH_3), 63.2 (CH), 165.0 (C), 169.7 (C), 173.2 (C) ppm. MS (EI, 70 eV): *m/z* (%): 184 (12) $[M]^{+\cdot}$, 140 (70) $[M - H_2NCO]^{+\cdot}$, 123 (8) $[M - H_2NCO - NH_3]^{+\cdot}$, 97 (100) $[M - H_2NCO - HNCO]^{+\cdot}$, 82 (6), 57 (18), 42 (17). $C_7H_{12}N_4O_2$ (184.2): calcd. C 45.64, H 6.57, N 30.42; found C 45.39, H 6.66, N 30.22.

5-Imino-1-methyl-L-proline Amide (12-H): To a suspension of **8** (0.80 g, 2.9 mmol) in anhydrous DMF (15 mL) was added 10% Pd/C (100 mg, oxidized form, VWR). The mixture was vigorously stirred for several hours under an atmosphere of hydrogen. The starting material gradually dissolved in the course of the deprotection procedure. The reaction mixture was filtered through Celite; the filter cake was washed with anhydrous DMF (10 mL). The solvent was evaporated in vacuo, and the residue was taken up in methanol. The title compound was precipitated as a colorless solid by addition of anhydrous ether. A very hygroscopic substance was filtered off, washed with diethyl ether, and dried in vacuo. Yield: 0.35 g (85%). ^1H NMR (250 MHz, [D_6]DMSO): δ = 1.77 (m_c, 1 H, 3-H), 2.15 (m_c, 1 H, 3-H), 2.36–2.51 (m, 2 H, 4-H), 2.69 (s, NMe, 3 H), 3.97 (dd, *J* = 8.8, 3.9 Hz, 1 H, 2-H), ca. 5.8 (br. s, 1 H, C=NH), 7.4 (s, 1 H, $CONH_2$), 8.0 (s, 1 H, $CONH_2$) ppm. MS (EI, 70 eV): *m/z* (%) = 141 (8) $[M]^{+\cdot}$, 97 (100) $[M - H_2NCO]^{+\cdot}$, 82 (7), 57 (20), 42 (17). MS (CI, NH_3): *m/z* (%) = 142 (100) $[M + H]^+$, 283 (19) $[2M + H]^+$.

5-Benzyloxycarbonylimino-1-methyl-L-proline Amide (12-Z): A mixture of **12**-H (0.21 g, 1.5 mmol), ZOPfp (0.52 g, 1.6 mmol), *i*Pr_2NEt (0.19 g, 0.25 mL, 1.5 mmol), and *N*,*N*-dimethylacetamide (2.0 mL) was heated at 55 °C for 12 h. The solvent was evaporated in vacuo, the residue was taken up in ether and transferred onto a filter, washed with a small amount of cold water, then again with ether, and dried in vacuo; m.p. 149–151 °C. Yield: 0.27 g (66%). R_f = 0.50 (CH_2Cl_2/MeOH, 10:1). ^1H NMR (250 MHz, [D_6]DMSO): δ = 1.83 (m_c, 1 H, 3-H), 2.21 (m_c, 1 H, 3-H), 2.81 (s, NMe), 2.85 (m, 4-H, Σ 5 H), 4.18 (dd, *J* = 9, 4 Hz, 1 H, 2-H), 5.01 (s, 2 H, OCH_2), 7.31 (br. s, 1 H, $CONH_2$), 7.38 (s, 5 H, C_6H_5), 7.67 (s, 1 H, $CONH_2$) ppm. ^{13}C NMR (62.9 MHz, [D_6]DMSO): δ = 24.8 (CH_2), 30.2 (CH_2), 30.8 (CH_3), 64.0 (CH), 66.0 (CH_2O), 127.8 (CH), 128.0 (2 CH), 128.5 (2 CH), 137.6 (C), 162.5 (C), 172.4 (C), 174.1 (C) ppm. MS (EI, 70 eV): *m/z* (%) = 275 (16) $[M]^{+\cdot}$, 231 (28) $[M - H_2NCO]^{+\cdot}$, 168 (22) $[M - C_7H_7O]^{+\cdot}$, 97 (21), 91 (100). HRMS (EI): calcd. for $C_{14}H_{17}N_3O_3$ $[M]^{+\cdot}$ 275.1270; found 275.1269.

Acknowledgments

This work was financially supported by Bayer AG. The authors are grateful to Reinhard Machinek, Holm Frauendorf, and their coworkers for recording NMR and mass spectra. We thank Mrs. E. Pfeil for measuring the optical rotation values and Rene Kandler for helping with HPLC analyses.

[1] a) N. Katayama, S. Fukusumi, Y. Funabashi, T. Iwahi, H. Ono, *J. Antibiot.* **1993**, *46*, 606–613; b) Y. Funabashi, S. Tsubotani, K. Koyama, N. Katayama, S. Harada, *Tetrahedron* **1993**, *49*, 13–28.

[2] For the total syntheses of TAN-1057A/B, see: a) V. V. Sokolov, S. I. Kozhushkov, S. Nikolskaya, V. N. Belov, M. Es-Sayed, A. de Meijere, *Eur. J. Org. Chem.* **1998**, 777–783; b) C. Yuan, R. M. Williams, *J. Am. Chem. Soc.* **1997**, *119*, 11777–11784; c) for a total synthesis of TAN-1057A, see: V. N. Belov, M. Brands, S. Raddatz, J. Krüger, S. Nikolskaya, V. V. Sokolov, A. de Meijere, *Tetrahedron* **2004**, *60*, 7579–7589; for a review on the medicinal chemistry of natural antibacterials, see: d) F. von Nussbaum, M. Brands, B. Hinzen, S. Weigand, D. Häbich, *Angew. Chem.* **2006**, *118*, 5194–5254, *Angew. Chem. Int. Ed.* **2006**, *45*, 5072–5129; for a review on natural guanidine derivatives, see: e) R. G. S. Berlinck, *Nat. Prod. Rep.* **1999**, *16*, 339–365; for TAN-1057A/B analogues, see: f) L. Zhang, C. U. Kim, L. Xu, *Tetrahedron Lett.* **2007**, *48*, 3273–3275; g) L. Xu, L. Zhang, C. M. Bryant, C. U. Kim, *Tetrahedron Lett.* **2003**, *44*, 2601–2604; h) L. Zhang, L. Xu, C. U. Kim, *Tetrahedron Lett.* **2003**, *44*, 5871–5873; i) P. Lin, A. Ganesan, *Synthesis* **2000**, *14*, 2127–2130; j) M. Brands, R. Endermann, R. Gahlmann, J. Krüger, S. Raddatz, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 241–245; k) M. Brands, Y. C. Grande, R. Endermann, R. Gahlmann, J. Krüger, S. Raddatz, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2641–2645; l) M. Brands, R. Endermann, R. Gahlmann, J. Krüger, S. Raddatz, J. Stoltefuß, V. N. Belov, S. Nizamov, V. V. Sokolov, A. de Meijere, *J. Med. Chem.* **2002**, *45*, 4246–4253; m) R. M. Williams, C. Yuan, V. J. Lee, S. Chamberland, *J. Antibiot.* **1998**, *51*, 189–201; n) M. Kordes, M. Brands, M. Es-Sayed, A. de Meijere, *Eur. J. Org. Chem.* **2005**, 3008–3016; o) N. Aguilar, J. Krüger, *Molecules* **2002**, *7*, 469–474.

[3] Acyclic amidines with *N*-[alkyl(aryl)amino]sulfonyl- and *N*′-alkoxycarbonyl substituents have been described: G. Hamprecht, R.-D. Acker, E. Hädicke, *Liebigs Ann. Chem.* **1985**, 2363–2370.

[4] H. Ueno, A. Maruyama, M. Miyake, E. Nakao, K. Nakao, K. Umezu, I. Nitta, *J. Med. Chem.* **1991**, *34*, 2468–2473.
[5] Cf.: M. Protiva, V. Řeřicha, J. O. Jilek, *Chem. Listy* **1954**, *48*, 1210–1211.
[6] C. Ressler, H. Ratzkin, *J. Org. Chem.* **1961**, *26*, 3356–3360.
[7] T. Itoh, *Bull. Chem. Soc. Jpn.* **1963**, *36*, 25–29.
[8] E. W. Della, H. Gangodawila, *Aust. J. Chem.* **1989**, *42*, 1485–1492.
[9] Methyl iodide in the presence of Ag_2O in DMF has been shown to provide full conversion of *N*-Z and *N*-Boc amino acids into the corresponding *N*-methyl derivatives without appreciable racemization: R. K. Olsen, *J. Org. Chem.* **1970**, *35*, 1912–1915.
[10] L. Grehn, M. L. S. Almeida, U. Ragnarsson, *Synthesis* **1988**, 992–994. Acetylation of compound **8** gave a product that was unstable in the presence of water. Carbamoylation in the presence of water was found to be ineffective.
[11] These are standard conditions for the peptide coupling reaction (e.g., C. Gao, C.-H. Lin, C.-H. L. Lo, S. Mao, P. Wirsching, R. A. Lerner, K. D. Janda, *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 11777–11782).
[12] L. Castellanos, C. Duque, S. Zea, A. Espada, J. Rodrigues, C. Jiménez, *Org. Lett.* **2006**, *8*, 4967–4970. In this report, (*S*)-5-imino-1-methylproline and the corresponding methyl ester were prepared in five and six steps, respectively, in 42% overall yield.
[13] R. E. Mitchell, K. L. Teh, *Org. Biomol. Chem.* **2005**, *3*, 3540–3543.
[14] a) T. J. Hagen, A. A. Bergmanis, S. W. Kramer, K. F. Fok, A. E. Schmelzer, B. S. Pitzele, L. Swenton, G. M. Jerome, C. M. Kornmeier, W. M. Moore, L. F. Branson, J. R. Connor, P. T. Manning, M. G. Currie, E. A. Hallinan, *J. Med. Chem.* **1998**, *41*, 3675–3683; b) S. Tsymbalov, T. J. Hagen, W. M. Moore, G. M. Jerome, J. R. Connor, P. T. Manning, B. S. Pitzele, E. A. Hallinan, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3337–3339.

Received: March 23, 2011
Published Online: June 8, 2011

