Convergent Syntheses of *N*-Boc-Protected (2*S*,4*R*)-4-(*Z*)-Propenylproline and 5-Chloro-1-(methoxymethoxy)pyrrol-2-carboxylic Acid − Two Essential Building Blocks for the Signal Metabolite Hormaomycin

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An efficient and scalable synthesis of enantiomerically pure *N*-Boc-protected 4-(*Z*)-propenylproline (**15**) using the conventional Wittig reaction to construct the double bond has been developed [11% yield over 8 steps from *N*-Boc-protected (2*S*,4*R*)-4-hydroxyproline, **7**]. The *O*-MOM-protected 5-chloro-1-hydroxypyrrole-2-carboxylic acid [Chpca(MOM)-OH (**29**)] was prepared along a reasonably efficient synthetic route applying the thermal rearrangement of 2-azido-6-chloropyridine *N*-oxide (**22**) as a key step in fairly good overall yield [9% over 7 steps from easily accessible 2,6-dichloropyridine *N*-oxide (**21**)]. The suitability of the MOM-protected *N*-hydroxy group during the preparation of the *N*-hydroxypyrroles functionalized at C-2, was confirmed by the successful synthesis of Chpca-(3-Ncp)Ala-OFM **33** obtained from the acylated amino ester Chpca(MOM)-(3-Ncp)Ala-OFM **32**, which was selectively deprotected leaving the sensitive *N*-hydroxypyrrole unit intact.

Introduction

The cyclic depsipeptide hormaomycin **1** has a unique structure and quite an interesting spectrum of biological activities.[1] Besides one residue of the proteinogenic amino acid isoleucine [(*S*)-Ile], it contains two units of 3-methylphenylalanine [(βMe)Phe], one of (2*R*)-*allo*-threonine [*a*-Thr] as well as two moieties of 3-(*trans*-2′-nitrocyclopropyl)alanine [(3-Ncp)Ala] and one of 4-(*Z*)-propenylproline [(4-PE)Pro]. The side chain of **1** is terminated with a residue of 5-chloro-1-hydroxypyrrole-2-carboxylic acid [Chpca] (Figure 1). The latter three have never been found in any natural product before. The importance of the (3-Ncp)Ala and (βMe)Phe residues of hormaomycin for its biological activity is unclear.[2] However, very early during the investigations concerning hormaomycin it was recognized that the residues of [(4-PE)Pro and Chpca are crucially important for the two main biological activities of hormaomycin: its essentially selective antibiotic activity against Coryneform bacteria and the morphogenous action on the producing strain and other Streptomyces species.[2a,2c,3] For our ongoing development of a synthetic access to hormaomycin and a representative series of its biologically significant analogues[2c,4] we were in need of suitably protected (2*S*,4*R*)-4-(*Z*)-propenylproline as well as 5-chloro-1-hydroxypyrrole-2-carboxylic acid. Since no synthesis of either of these compounds had ever been reported, we developed suitable convergent accesses to *N*-Boc-protected (2*S*,4*R*)-4-(*Z*)-propenylproline (**15**) and *O*-methoxymethyl-(MOM-)protected 5-chloro-1-hydroxypyrrol-2-carboxylic acid (**29**).

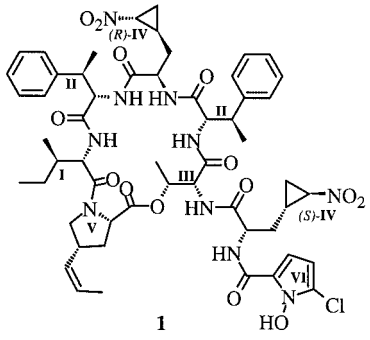

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Figure 1. Structure and absolute configuration of hormaomycin **1**. **I** (*S*)-Ile; **II** (2*S*,3*R*)-(βMe)Phe; **III** (2*R*)-*a*-Thr; **IV** (1′*R*,2′*R*)-(3-Ncp)Ala; **V** (2*S*,4*R*)-4-(*Z*)-(4-PE)Pro; **VI** Chpca

Results and Discussion

Initially, the *N*-protected *tert*-butyl (*S*)-(*E*)-propylidenepyroglutamate **4** was chosen as a starting material for the synthesis of the target compound **15** (Scheme 1). A deconjugating isomerization of compound **4** was expected to give the corresponding 4-propenylpyroglutamate, which might be transformed to the appropriate 4-propenylproline. At least for simple models studied before, this transformation

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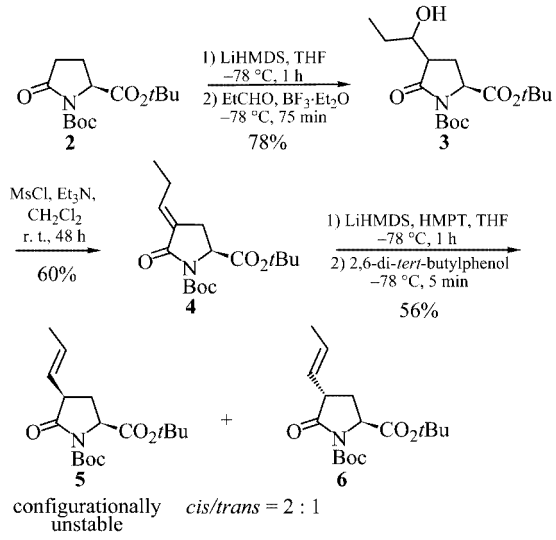
often proceeded in such a way that the (*E*)-α,β-unsaturated esters or amides gave the (*Z*)-deconjugated products, and in contrast a (*Z*)-configured conjugated double bond was converted into an (*E*)-configured double bond with good selectivity.[5] The *N*-Boc-protected *tert*-butyl (*S*)-4-(*E*)-propylidenepyroglutamate **4**[6] was prepared as described by Ezquerra et al.[7] for the corresponding ethyl ester. Towards this, the enolate of the *tert*-butyl ester **2**,[8] generated by treatment with LiHMDS in THF, in the presence of 1.15 equivalent of $BF_3{\cdot}Et_2O$ at −78 °C was added to propanal to give the known (hydroxypropyl)pyroglutamate derivative **3**[9] as a partially separable mixture of three out of four possible diastereomers (the configuration at C-2 was retained) in much better yield (78 rather than 28%) than reported before.[7]



Scheme 1

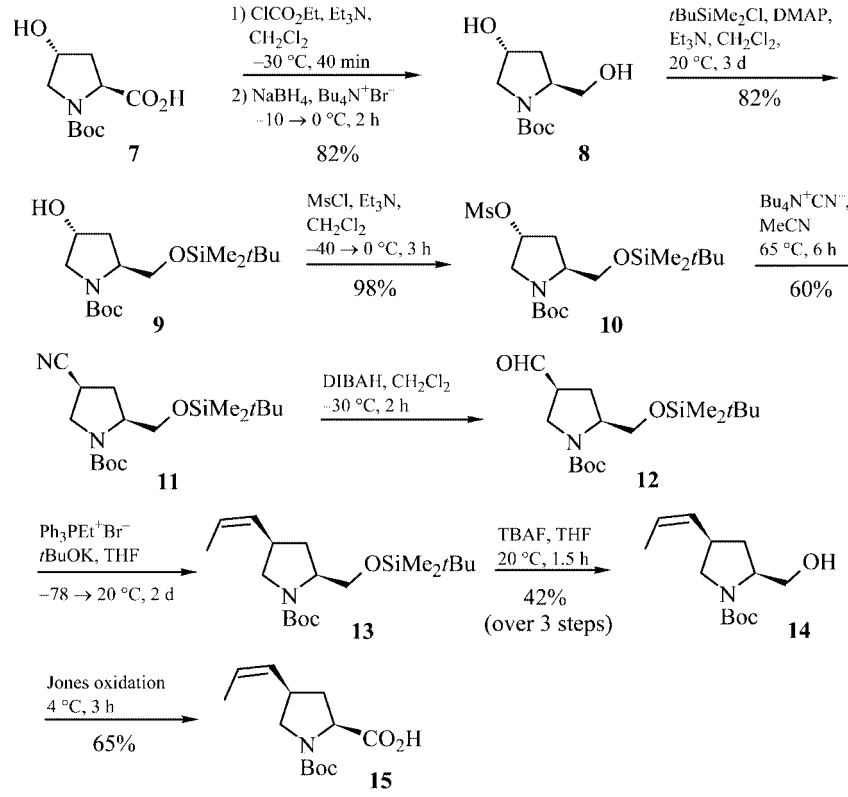
Compound **3** was treated with an excess of mesyl chloride and triethylamine in CH_2Cl_2, and the resulting mixture of (*E*)- and (*Z*)-diastereomeric 4-propylidenepyroglutamate derivatives was separated by column chromatography to give the required (*E*)-isomer **4** (60%) along with a small amount of the (*Z*)-isomer (4%). The configuration of the double bond in the main product was proved by a NOESY experiment. The *N*-protected 4-(*E*)-propylidenepyroglutamate (*S*)-**4** was treated with a slight excess of LiHMDS in THF/HMPT mixture at −78 °C, and the resulting enolate was quenched with 2,6-di-*tert*-butylphenol as a sterically encumbered proton source. This method of enolate quenching is known to give preferentially *cis*-isomers because of the protonation from the least hindered side.[10] The diastereomeric mixture obtained in this case was separated by column chromatography to give the *cis*- **5** (37%) and the *trans*-isomer **6** (19%). An attempt to remove the last 10% of the *trans*-isomer from **5** failed because of its configurational instability, which led to tailing on the column due to 30−40% epimerization to the thermodynamically more stable *trans*-isomer upon each usual flash chromatography. Surprisingly, the NMR spectra of these products disclosed that only the (*E*)-isomer had been formed. Thus, this deconjugating isomerization provides access to yet unknown 4-alkenyl-substituted pyroglutamic acids (and consequently alkenyl-substituted glutamic acids, prolines and leucines). However, the "wrong" configuration of the double bond in **5** and the configurational instability precluded to use this procedure for the synthesis of *N*-Boc-protected 4-(*Z*)-propenylproline **15**.

In an alternative approach, the conventional Wittig reaction was used to construct the double bond (Scheme 2). The *N*-Boc-protected 4-hydroxyproline **7** was treated with ethyl chloroformate and triethylamine in CH_2Cl_2 at −30 °C, and the mixed anhydride was reduced with aqueous $NaBH_4$ in the presence of tetra-*n*-butylammonium bromide as a phase-transfer catalyst to give the *N*-Boc-protected 4-hydroxyprolinol **8** in 82% yield. The primary hydroxy group of **8** was selectively protected as a *tert*-butyldimethylsilyl ether **9** (82% yield) as described by Williams et al.[11] Treatment of **9** with mesyl chloride and triethylamine in CH_2Cl_2 gave the mesylate **10** in almost quantitative yield. This in turn was transformed into the nitrile **11** by treatment with tetrabutylammonium cyanide in MeCN at 65 °C for 6 h in reproducible (yield around 60%) on a 30−50 g scale.[12]

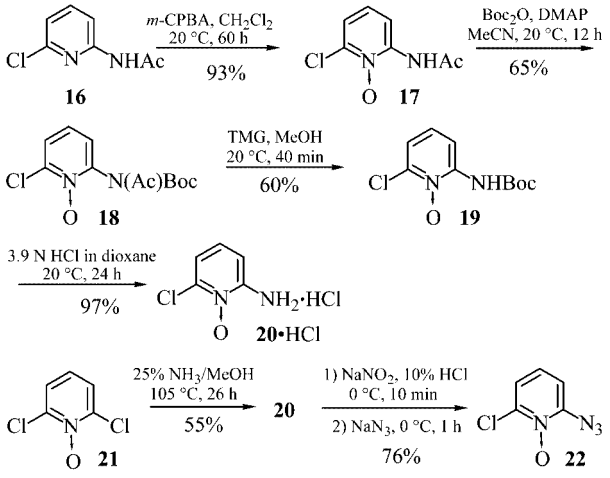
The latter was reduced to the configurationally unstable crude aldehyde **12** with DIBAH in 97% yield. By slow addition of **12** to 3−4 equivalents of the ylide generated from ethyltriphenylphosphonium bromide with potassium *tert*-butoxide[13] in THF at −78 °C, the epimerization at C-4 was significantly decreased. The fully protected 4-(*Z*)-propenylprolinol **13**, which contained only traces of the (2*S*,4*S*)-epimer was obtained with excellent *E*/*Z*-selectivity (*E*/*Z* ratio 1:14−1:30). The *tert*-butyldimethylsilyl group was smoothly removed with tetrabutylammonium fluoride in THF to furnish the alcohol **14** in 42% yield over 3 steps (from **11**). This primary alcohol was oxidized with 10 equivalents of Jones reagent in acetone at 4 °C to give the desired *N*-Boc-protected 4-(*Z*)-propenylproline **15** in 65% yield (11% overall yield from **7** over 8 steps).[14] The high diastereo- and enantiomeric purity of this product was confirmed by HPLC (*d.r.* > 98:1, *e.e.* 97%).[15] This same synthetic sequence was also successfully applied for the diastereo- and enantioselective preparation of the deuterium labeled H-(4-PE)Pro-OH.[16]

N-Hydroxy- and *N*-alkoxypyrroles apparently have not attracted much attention of chemists. Only the preparation of several 2-cyano-1-hydroxypyrroles by thermal decomposition of the corresponding 3-unsubstituted 2-azidopyridine *N*-oxides in benzene, has been described by Abramovitch et al.[17] and this was used as a lead motif for the preparation of the suitably protected 5-chloro-1-hydroxypyrrole-2-carboxylic acid.

Since an attempted direct oxidation of 2-amino-6-chloropyridine[18] with *m*-chloroperbenzoic acid (*m*-CPBA) according to the protocol of Pentimalli[19] unexpectedly did not give the desired *N*-oxide **20**, it was prepared from 2-acetamido-6-chloropyridine (**16**)[20] or alternatively from 2,6-dichloropyridine *N*-oxide[21] (**21**) (Scheme 3).



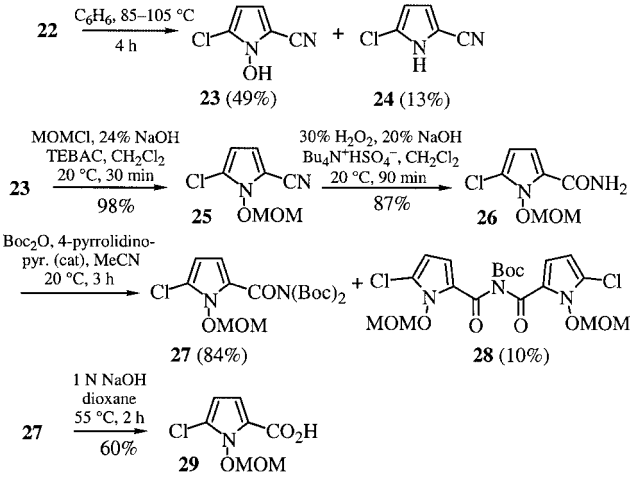
Scheme 2



Scheme 3

2-Acetamido-6-chloropyridine (**16**) could be oxidized with *m*-CPBA in dichloromethane to give the *N*-oxide **17** (93%) which was *N*-acylated with Boc_2O to furnish the diacylated amine **18** in 65% yield. Deacetylation to the *N*-Boc-protected amine **19** in 60% yield was achieved with *N,N,N′,N′*-tetramethylguanidine (TMG) in methanol. Removal of the Boc group from the latter with 3.9 M HCl in 2-propanol led to the desired amine as the hydrochloride **20**·HCl in 97% yield. More efficiently, the treatment of 2,6-dichloropyridine *N*-oxide **21** with 25% NH_3 in methanol in a sealed tube at 100 °C for 24 h gave **20** as the free base in a single step in 55% yield. Subsequent diazotization of **20** followed by treatment with sodium azide provided 2-azido-6-chloropyridine *N*-oxide **22** in 76% yield.

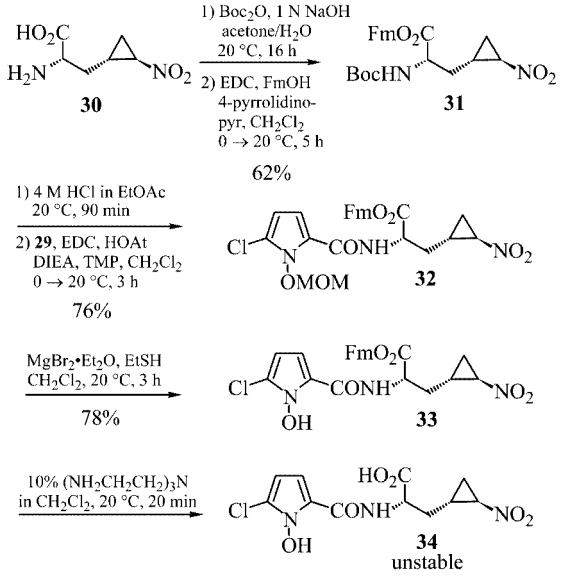
Thermal decomposition of the latter in degassed benzene furnished 5-chloro-2-cyano-1-hydroxypyrrole **23** in 49% yield along with the deoxygenated pyrrole **24** (13%) (Scheme 4). All attempts to hydrolyze **23** under different conditions led only to its decomposition. Therefore the *N*-hydroxy compound **23** was transformed into a meth-



Scheme 4

oxymethyl ether **25**. Hydrolysis of the nitrile group in **25** with sodium hydroperoxide under PTC conditions according to a protocol of Cacchi et al.[22] gave the amide **26** (all attempts to hydrolyze **25** and **26** to the respective acids were also unsucessful). This intermediate was acylated with Boc_2O in acetonitrile in the presence of 4-pyrrolidinopyridine (4-PP) to give the bis(*tert*-butoxycarbonyl)amide **27** (84%) along with the *N*-Boc-bis(pyrrolecarbonyl)amine **28** as a side product (10%). Further hydrolysis of **27** under alkaline conditions[23] then gave *O*-MOM-protected Chpca-OH **29** (43% overall yield over 4 steps from **23**).

To test the applicability of **29** towards the synthesis of hormaomycin **1**, the fully protected dipeptide-like side chain of **1** was synthesized and deprotected (Scheme 5). (2*S*,1′*R*,2′*R*)-H-(3-Ncp)Ala-OH **30**[24] was first protected with Boc_2O and then esterified with 9-fluorenylmethanol (FmOH) using EDC in the presence of 4-pyrrolidinopyridine to yield **31** (62% over 2 steps) (Scheme 5). The latter, after removal of the Boc group, was coupled with *O*-MOM-protected Chpca-OH **29** to give the *N*-pyrrolcarbonylamino ester **32** in 76% yield. Removal of the MOM group succeeded by treatment with $MgBr_2{\cdot}Et_2O$ in CH_2Cl_2 (78%).[25] The resulting **33** was further transformed into the free acid **34**, by treatment with tris-(2′-aminoethyl)amine, however, it was too unstable (complete polymerization in THF or $CDCl_3$ solution within 30 min) to be used in any further peptide condensation step. Eventually, the side chain of hormaomycin **1** was attached to the preformed ring part in a stepwise manner, before finally cleaving off the MOM protective group under conditions mentioned above.[4]



Scheme 5

Conclusion

The newly developed efficient diastereo- and enantioselective routes to *N*-Boc-protected 4-(*Z*)-propenylproline **15** as well as *O*-MOM-protected 5-chloro-1-hydroxypyrrol-2-carboxylic acid (**29**) can easily be extended and used for the synthesis of related potentially pharmacologically relevant compounds as for example new analogues of kainic acid,[26] compounds related to the new inhibitor of influenza, or neuraminidase A-315675[27] besides new modified analogues of hormaomycin **1**.

Experimental Section

General Aspects: ^1H NMR spectra: Bruker AM 250 (250 MHz), Varian Inova 300 (300 MHz). ^1H chemical shifts are reported in ppm relative to residual peaks of deuterated solvents or tetramethylsilane. Higher order NMR spectra were approximately interpreted as first-order spectra, if possible. The observed signal multiplicities are characterized as follows: s singlet, d doublet, t triplet, q quadruplet, quin quintet, m multiplet, br broad, Ar-H aryl-H. ^{13}C NMR spectra [additional DEPT (Distortionless Enhancement by Polarization Transfer) or APT (Attached Proton Test)]: Bruker AM 250 (62.9 MHz), Varian Inova 300 (75.5 MHz) instruments. ^{13}C chemical shifts are reported relative to peaks of the respective solvent or tetramethylsilane. The following abbreviations are used: DEPT: + primary or tertiary (positive signal in DEPT), − secondary (negative signal in DEPT), C_{quat} quaternary (no signal in DEPT); APT: + primary or tertiary (positive signal in APT), − secondary or quaternary (negative signal in APT). IR spectra: Bruker IFS 66 (FT-IR) spectrometer, samples measured as KBr pellets or oils between KBr plates. MS: EI-MS: Finnigan MAT 95, 70 eV, high resolution EI-MS spectra with perfluorokerosene as reference substance. ESI-MS: Finnigan LCQ. MS (HR-EI): preselected ion peak matching at $R >> 10000$ to be within ±2 ppm of the exact masses. HPLC: pump: Kontron 322 system, detector: Kontron DAD 440, mixer: Kontron HPLC 360, data system: Kontron Kromasystem 200, columns: Knauer Nucleosil-100 C18 (5 μm, 3 mm × 250 mm). Optical rotations: Perkin−Elmer 241 digital polarimeter, 1-dm cell; optical rotation values are given in 10^{-1} deg cm^2 g^{-1}; concentrations (*c*) are given in g/100 mL. M.p.: Büchi 510 capillary melting point apparatus, uncorrected values. TLC: Macherey−Nagel precoated sheets, 0.25 mm Sil G/UV_{254}. The chromatograms were viewed under UV light and/or by treatment with phosphomolybdic acid (10% in ethanol), or ninhydrin (0.2% in ethanol). Column chromatography: Merck silica gel, grade 60, 230−400 mesh and Baker silica gel, 40−140 mesh. Preparative TLC: Macherey−Nagel, silica gel SIL G/UV_{254}, layer thickness 0.25 mm (100 × 200 mm or 200 × 200 mm). Elemental analyses: Mikroanalytisches Laboratorium des Instituts für Organische und Biomolekulare Chemie der Universität Göttingen. Starting materials: Anhydrous solvents were prepared according to standard methods by distillation over drying agents and were stored under argon. All other solvents were distilled before use. All reactions were carried out with magnetic stirring and, if air or moisture sensitive, in flame-dried glassware under argon or nitrogen. Organic extracts were dried with anhydrous $MgSO_4$. *tert*-Butyl (*S*)-*N*-(*tert*-butyloxycarbonyl)pyroglutamate (**2**),[28] (2*S*,4*R*)-(*N*-*tert*-butyloxycarbonyl)-4-hydroxyproline (**7**),[29] (2*S*,4*R*)-(*N*-*tert*-butyloxycarbonyl)-4-hydroxyprolinol *tert*-butyldimethylsilyl ether (**9**),[11] tetrabutylammonium cyanide,[30] 2-acetamino-6-chloropyridine (**16**),[20] 2,6-dichloropyridine *N*-oxide (**21**)[21] were prepared as described elsewhere. (2*S*,1′*R*,2′*R*)-3-(2′-Nitrocyclopropyl)alanine was kindly provided by O. V. Larionov (Göttingen).[24]

***tert*-Butyl (2*S*)-*N*-Boc-4-(1′-hydroxypropyl)pyroglutamate (3):** A solution of LiHMDS in THF, prepared by addition of a 2.47 M

BuLi solution in hexane (2.33 mL, 5.75 mmol) to a solution of HMDS (1.30 mL, 6.16 mmol) in THF (18 mL) at −78 °C followed by stirring of the resulting mixture at 4 °C for 1 h, was added to a solution of **2** (1.43 g, 5.01 mmol) in THF (40 mL) at −78 °C, and the resulting mixture was stirred at the same temperature for an additional 1 h. A solution of propionaldehyde (0.42 mL, 5.79 mmol) and $BF_3{\cdot}Et_2O$ (0.73 mL, 5.76 mmol) in THF (18 mL) was then added, and stirring continued at the same temperature for 75 min. The reaction was then quenched with saturated NH_4Cl (30 mL), and the mixture was diluted with Et_2O (250 mL). The organic layer was separated, washed with water (3 × 40 mL), 0.5 M H_2SO_4 (3 × 40 mL), water (3 × 40 mL), brine (2 × 30 mL), dried, filtered and concentrated under reduced pressure. The residue was separated by column chromatography (EtOAc/hexane, 1:3) to give one pure diastereomer (785 mg, 46%) as a colorless oil, and an inseparable mixture of two other diastereomers in a ratio of 1:3 [550 mg, 78% overall yield of **3**]. No attempts to elucidate the configuration of these products were made. The pure diastereomer: R_f = 0.23 (EtOAc/hexane, 1:3). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.98 (t, J = 7.3 Hz, 3 H, 3′-H), 1.48 [s, 9 H, $C(CH_3)_3$], 1.50 [s, 9 H, $C(CH_3)_3$], 1.84−2.12 (m, 2 H, 3-H), 2.63 (dt, J = 12.2, 8.7 Hz, 1 H, 4-H), 3.59−3.70 (m, 1 H, 1′-H), 4.24 (s, 1 H, OH), 4.44 (d, J = 8.0 Hz, 1 H, 2-H). The signal of 2′-H overlapped with that of the *tert*-butyl group. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 8.8 (+, C-3′), 24.9 (−, C-2′), 26.7 (−, C-3), 27.4 [+, $C(CH_3)_3$], 27.5 [+, $C(CH_3)_3$], 45.5 (+, C-4), 57.4 (+, C-2), 72.7 (+, C-1′), 82.1 [C_{quat}, $C(CH_3)_3$], 83.2 [C_{quat}, $C(CH_3)_3$], 148.5 (C_{quat}, NCO_2), 169.6 (C_{quat}, C-1), 176.1 (C_{quat}, C-5). The mixture of diastereomers: R_f = 0.15 (EtOAc/hexane, 1:3). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.99 (t, J = 7.3 Hz, 3 H, 3′-H), 1.15−1.30 (m, 0.4 H, 2′-H_a), 1.48 [s, 9 H, $C(CH_3)_3$], 1.50 [s, 9 H, $C(CH_3)_3$], 1.85−2.10 (m, 0.6 H, 3-H), 2.31−2.80 (m, 2 H, 3-H, 4-H), 3.49−3.70 (m, 1 H, 1′-H), 4.12 (s, 1 H, OH), 4.35 (dd, J = 8.0, 8.0 Hz, 0.7 H, 2-H), 4.43 (dd, J = 1.2, 10.4 Hz, 0.3 H, 2-H). The signal of 2′-H overlapped with that of the *tert*-butyl group. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 8.5, 9.0 (+, C-3′), 18.5, 21.6 (−, C-2′), 24.6 (−, C-3), 27.0, 27.1 [+, $C(CH_3)_3$], 27.7, 27.8 [+, $C(CH_3)_3$], 46.7, 47.2 (+, C-4), 57.8, 57.9 (+, C-2), 70.0, 72.9 (+, C-1′), 82.1, 82.3 [C_{quat}, $C(CH_3)_3$], 83.2, 83.8 [C_{quat}, $C(CH_3)_3$], 148.9, 149.0 (C_{quat}, NCO_2), 169.8, 170.5 (C_{quat}, C-1), 174.6, 175.9 (C_{quat}, C-5).

***tert*-Butyl 2-(*S*)-*N*-Boc-4-(*E*)-propylidenepyroglutamate (4):** Et_3N (4.00 mL, 28.56 mmol) followed by mesyl chloride (0.23 mL, 2.97 mmol) was added dropwise to a stirred ice-cold solution of the mixture of diastereomers of **3** (0.55 g, 1.60 mmol) in CH_2Cl_2 (20 mL), and the mixture was then allowed to warm to 20 °C. Stirring was continued for an additional 48 h, and the reaction was then quenched with water (3 mL). EtOAc (80 mL) was added, and the organic layer was washed with water (4 × 20 mL) and brine (2 × 20 mL), dried, filtered and concentrated under reduced pressure. The resulting oily residue was identical with the one obtained by reaction of the pure diastereomer of **3** (0.785 g, 2.29 mmol) with Et_3N (5.8 mL, 41.44 mmol) and mesyl chloride (0.32 mL, 4.13 mmol) in CH_2Cl_2 (20 mL). Both portions were combined and purified by column chromatography (twice: first EtOAc/hexane, 3:7, then EtOAc/hexane, 1:3) to give **4** (760 mg, 60%) as a faintly tan solid and the (*Z*)-isomer (55 mg, 4%). The configuration of the main product was confirmed by NOESY NMR measurement.

4: R_f = 0.55 (EtOAc/hexane, 3:7). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.01 (t, J = 7.5 Hz, 3 H, 3′-H), 1.42 [s, 9 H, $C(CH_3)_3$], 1.45 [s, 9 H, $C(CH_3)_3$], 2.11 (dddd, J = 7.5, 7.5, 7.5, 7.5 Hz, 2 H, 2′-H), 2.42−2.54 (m, 1 H, 3-H_a), 2.89−3.09 (m, 1 H, 3-H_b), 4.45 (dd, J = 7.8, 3.5 Hz, 1 H, 2-H), 6.57−6.70 (m, 1 H, 1′-H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 12.6 (+, C-3′), 22.6 (−, C-2′), 25.5 (−, C-3), 27.7 [+, $C(CH_3)_3$], 27.8 [+, $C(CH_3)_3$], 56.4 (+, C-2), 82.0 [C_{quat}, $C(CH_3)_3$], 83.0 [C_{quat}, $C(CH_3)_3$], 127.9 (C_{quat}, C-4), 140.2 (+, C-1′), 149.8 (C_{quat}, NCO_2), 166.2 (C_{quat}, C-1), 170.2 (C_{quat}, C-5).

(*Z*)-isomer: R_f = 0.75 (EtOAc/hexane, 3:7). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.01 (t, J = 7.5 Hz, 3 H, 3′-H), 1.45 [s, 9 H, $C(CH_3)_3$], 1.51 [s, 9 H, $C(CH_3)_3$], 2.43−2.58 (m, 1 H, 3-H_a), 2.75 (dddd, J = 7.5, 7.5, 7.5, 7.5 Hz, 2 H, 2′-H), 2.89−3.09 (m, 1 H, 3-H_b), 4.42 (dd, J = 7.8, 3.5 Hz, 1 H, 2-H), 5.92−6.06 (m, 1 H, 1′-H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.7 (+, C-3′), 20.6 (−, C-2′), 27.8 [+, $C(CH_3)_3$], 27.9 [+, $C(CH_3)_3$], 29.1 (−, C-3), 56.5 (+, C-2), 82.0 [C_{quat}, $C(CH_3)_3$], 83.0 [C_{quat}, $C(CH_3)_3$], 126.0 (C_{quat}, C-4), 144.8 (+, C-1′), 150.1 (C_{quat}, NCO_2), 165.9 (C_{quat}, C-1), 170.2 (C_{quat}, C-5).

***tert*-Butyl (2*S*,4*S*)-*N*-Boc-4-(*E*)-(1′-propenyl)pyroglutamate (5) and *tert*-Butyl (2*S*,4*R*)-*N*-Boc-4-(*E*)-(1′-propenyl)pyroglutamate (6):** A solution of LiHMDS in THF/HMPT, prepared by addition of a 2.47 M BuLi solution in hexane (0.54 mL, 1.33 mmol) to a solution of HMDS (0.33 mL, 1.56 mmol) and HMPT (0.356 g, 1.99 mmol) in THF (5 mL) at −78 °C followed by stirring of the resulting mixture at 4 °C for 15 min, was added dropwise to a solution of **4** (0.375 g, 1.15 mmol) in THF (5 mL) at −78 °C within 20 min, and the mixture was stirred at the same temperature for an additional 1 h. Then a solution of 2,6-di-*tert*-butylphenol (0.713 g, 3.46 mmol) in THF (1 mL) was added within 10 min, and then a saturated aqueous NH_4Cl solution (ca. 8 mL). The mixture was allowed to warm to 20 °C and diluted with Et_2O (50 mL). The organic layer was separated, washed with water (3 × 40 mL), 0.5 M H_2SO_4 (3 × 40 mL), water (3 × 40 mL), brine (2 × 30 mL), dried, filtered and concentrated under reduced pressure. The residue containing the mixture of diastereomers and 2,6-di-*tert*-butylphenol was separated by column chromatography (twice, EtOAc/hexane, 1:3) to give **5** (140 mg, 37%) as a slightly yellow oil and **6** (70 mg, 19%) as a colorless solid. Compound **5** contained a little of another diastereomer (according to TLC; it was not visible in the ^{1}H NMR spectrum), and an attempt to remove this impurity by additional column chromatography was made. As the (2*S*,4*S*)-isomer **5** apparently isomerized to the other diastereomer, only material of essentially the same quality (70 mg) together with the (2*S*,4*R*)-isomer **6** (40 mg) and a mixed fraction (25 mg) were obtained.

5: R_f = 0.38 (EtOAc/hexane, 1:3). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.47 [s, 9 H, $C(CH_3)_3$], 1.50 [s, 9 H, $C(CH_3)_3$], 1.66 (dd, J = 5.0, 1.3 Hz, 3 H, 3′-H), 1.86 (dd, J = 12.5, 6.5 Hz, 1 H, 3-H_a), 2.53 (ddd, J = 13.3, 6.5, 6.5 Hz, 1 H, 3-H_b), 3.09−3.23 (m, 1 H, 4-H), 4.38 (dd, J = 9.0, 5.8 Hz, 1 H, 2-H), 5.30−5.52 (m, 1 H, 1′-H), 5.52−5.72 (m, 1 H, 2′-H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 17.8 (+, C-3′), 27.7 [+, 2 × $C(CH_3)_3$], 28.6 (−, C-3), 45.7 (+, C-4), 58.0 (+, C-2), 82.0 [C_{quat}, $C(CH_3)_3$], 83.1 [C_{quat}, $C(CH_3)_3$], 126.3 (+, C-2′), 129.3 (+, C-1′), 149.4 (C_{quat}, NCO_2), 170.1 (C_{quat}, C-1), 173.6 (C_{quat}, C-5).

6: R_f = 0.42 (EtOAc/hexane, 1:3), m.p. 70−71 °C, $[\alpha]_D^{20}$ = 7.1 (c = 0.31, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 2979 cm^{-1}, 2934, 1781, 1743, 1708, 1457, 1367, 1296, 1221, 1155. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.48 [s, 9 H, $C(CH_3)_3$], 1.50 [s, 9 H, $C(CH_3)_3$], 1.71 (dd, J = 6.3, 1.3 Hz, 3 H, 3′-H), 2.04−2.31 (m, 2 H, 3-H), 3.19−3.24 (m, 1 H, 4-H), 4.44 (dd, J = 9.0, 1.8 Hz, 1 H, 2-H), 5.47 (dd, J = 9.0, 1.3 Hz, 1 H, 1′-H), 5.63 (dq, J = 1.3, 6.3 Hz, 1 H, 2′-H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 17.9 (+, C-3′), 27.77 [+, $C(CH_3)_3$], 27.79 [+, $C(CH_3)_3$], 28.7 (−, C-3), 44.7 (+, C-4), 57.5 (+, C-2), 82.2 [C_{quat}, $C(CH_3)_3$], 83.1 [C_{quat}, $C(CH_3)_3$], 126.0 (+, C-2′), 129.7 (+, C-1′), 149.4 (C_{quat}, NCO_2), 170.1 (C_{quat}, C-1), 173.6 (C_{quat}, C-5).

MS (ESI), positive *m/z* (%) = 348 (75) [M + Na^+]. Elemental analysis calcd. (%) for $C_{17}H_{27}NO_5$ (325.4): calcd. C 62.75, H 8.36, N 4.30; found C 62.59, H 8.60, N 4.04.

(2*S*,4*R*)-*N*-Boc-4-Hydroxyprolinol (8): To a solution of **7** (57.5 g, 248 mmol) and triethylamine (38.4 mL, 273 mmol) in CH_2Cl_2 (1000 mL) was added at −30 °C ethyl chloroformate (25 mL, 261 mmol), and the mixture was stirred for 40 min. To this mixture were added tetra-*n*-butylammonium bromide (8.5 g, 26.4 mmol) and then carefully, by small portions a suspension of $NaBH_4$ (40 g, 1057 mmol) in ice-cold water (50 mL). The reaction mixture was allowed to warm to −10 °C and stirred for 1 h. The temperature of the mixture was further increased to 0 °C, and stirring was continued at this temperature for 1 h. The pH value of the aqueous layer was then carefully adjusted to 5−6 with 50% acetic acid, and the mixture was filtered through Celite®. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The aqueous layer was discarded, and the combined organic fractions were dried, concentrated under reduced pressure, and the residue was purified by column chromatography (EtOAc/hexane, 7:3, R_f = 0.24) to give **8** (44.23 g, 82%) as a colorless solid. M.p. 53−55 °C (ref.[31] m.p. 55−58 °C), $[\alpha]_D^{20}$ = −58.8 (*c* = 1.05, EtOH) (ref.[31] $[\alpha]_D^{20}$= −58.87, *c* = 1.009, EtOH). IR (KBr): $\tilde{\nu}$ = 3381 cm^{-1}, 2981, 2942, 2899, 1653, 1412, 1160, 1041. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.47 [s, 9 H, $C(CH_3)_3$], 1.57−1.80 (m, 1 H, 3-H_a), 1.89−1.98 (br, 1 H, OH), 1.98−2.11 (m, 1 H, 3-H_b), 3.35−3.63 (m, 3 H, 2-H, 5-H), 3.70 (dd, *J* = 9.4, 9.4 Hz, 1 H, 1-H_a), 4.04−4.25 (m, 1 H, 1-H_b), 4.29−4.45 (m, 1 H, 4-H), 4.95−5.09 (br, 1 H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 28.3 [+, $C(CH_3)_3$], 37.3 (−, C-3), 54.9, 55.6 (−, C-5), 57.7, 58.6 (+, C-2), 63.8, 66.4 (−, C-1), 68.8 (+, C-4), 80.4 [C_{quat}, $C(CH_3)_3$], 155.0, 156.9 (C_{quat}, NCO_2).

(2*S*,4*R*)-*N*-Boc-*O*-TBDMS-4-Mesyloxyprolinol (10): To a solution of **9** (48.14 g, 145 mmol) and triethylamine (30.4 mL, 218 mmol) in CH_2Cl_2 (120 mL) at −40 °C was added mesyl chloride (15.2 mL, 196 mmol) within 10 min. The mixture was allowed to warm to 0 °C and stirred for an additional 3 h, before saturated $NaHCO_3$ (100 mL) was added. The reaction mixture was taken up with Et_2O (500 mL), the organic layer was washed with H_2O (3 × 100 mL), 1 M $NaHSO_4$ (3 × 100 mL), H_2O (2 × 100 mL), brine (2 × 100 mL) and dried. Concentration under reduced pressure gave **10** (58.2 g, 98%) as a light yellow oil. R_f = 0.53 (EtOAc/hexane, 1:2.3), $[\alpha]_D^{20}$ = −38.5 (*c* = 0.55, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2930 cm^{-1}, 2858, 1698, 1473, 1404, 1366, 1257, 1174, 1120. ^1H NMR (250 MHz, $CDCl_3$): δ = 0.01 [s, 6 H, $Si(CH_3)_2$], 0.85 [s, 9 H, $SiC(CH_3)_3$], 1.44 [s, 9 H, $C(CH_3)_3$], 2.30−2.49 (m, 2 H, 3-H), 3.02 (s, 3 H, CH_3), 3.44−3.63 (m, 2 H, 5-H), 3.63−4.15 (m, 3 H, 1-H, 2-H), 5.25−5.33 (m, 1 H, 4-H). ^{13}C NMR (75.5 MHz, $C_2D_2Cl_4$, 353 K): δ = −5.7 [+, $Si(CH_3)_2$], 17.8 (C_{quat}, SiC), 25.6 [+, $SiC(CH_3)_3$], 28.3 [+, $C(CH_3)_3$], 34.8 (−, C−3), 38.4 (+, SO_2Me), 52.4 (−, C-5), 57.0 (+, C-2), 63.4 (−, C-1), 78.9 (+, C-4), 79.6 [C_{quat}, $C(CH_3)_3$], 153.6 (C_{quat}, NCO_2). MS (ESI), positive: *m/z* (%) = 432 (91) [M + Na^+].

(2*S*,4*S*)-*N*-Boc-*O*-TBDMS-4-Cyanoprolinol (11): A sealed round-bottomed flask containing a solution of the mesyl ester **10** (52.8 g, 129 mmol) and tetra-*n*-butylammonium cyanide (72.0 g, 268 mmol) in anhydrous MeCN (50 mL) was placed in an oil-bath which was preheated to 65−68 °C. After stirring the contents of the flask for 6 h, the mixture was taken up with EtOAc/hexane, 1:4 (500 mL), washed with water (8 × 100 mL) and brine (2 × 50 mL), dried and filtered through a pad of silica gel (5 cm). The solvents were removed under reduced pressure, and the residue was purified by column chromatography (EtOAc/hexane, 1:3, R_f = 0.50) to give **11** (26.5 g, 60%) as a yellowish oil which solidified to a colorless solid upon seeding. M.p. 55−58 °C, $[\alpha]_D^{20}$ = −25.9 (*c* = 0.9, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2952 cm^{-1}, 2895, 2855, 2240, 1696, 1471, 1400, 1259, 1172, 1099. ^1H NMR (300 MHz, $C_2D_2Cl_4$, 358 K): δ = 0.10 [s, 6 H, $Si(CH_3)_2$], 0.94 [s, 9 H, $SiC(CH_3)_3$], 1.48 [s, 9 H, $C(CH_3)_3$], 2.29−2.46 (m, 2 H, 3-H), 2.96 (dddd, *J* = 8.2, 8.2, 8.2, 8.2 Hz, 1 H, 4-H), 3.42 (dd, *J* = 8.2, 10.6 Hz, 1 H, 5-H_a), 3.74 (dd, *J* = 3.0, 9.8 Hz, 1 H, 1-H_a), 3.79−3.95 (m, 2 H, 1-H_b, 2-H), 3.96 (dd, *J* = 8.2, 10.6 Hz, 1 H, 5-H_b). ^{13}C NMR (75.5 MHz, $C_2D_2Cl_4$, 358 K): δ = −5.6 [+, $Si(CH_3)_2$], 17.9 (C_{quat}, SiC), 25.7 [+, $SiC(CH_3)_3$], 26.3 (+, C-4), 28.2 [+, $C(CH_3)_3$], 31.9 (−, C-3), 49.8 (−, C-5), 57.8 (+, C-2), 62.9 (−, C-1), 80.0 [C_{quat}, $C(CH_3)_3$], 119.8 (C_{quat}, CN), 153.2 (C_{quat}, NCO_2). MS (CI), *m/z* (%) = 358 (8) [M + NH_4^+], 341 (100) [M + H^+]. Elemental analysis calcd. (%) for $C_{17}H_{32}N_2O_3Si$ (340.5): calcd. C 59.96, H 9.47, N 8.23; found C 60.29, H 9.55, N 8.04.

(2*S*,4*S*)-*N*-Boc-*O*-TBDMS-4-Formylprolinol (12): A 1 M solution of DIBAH in hexane (36.1 mL, 36.10 mmol) was added dropwise at −30 °C over 10 min to a stirred solution of the cyanide **11** (9.10 g, 26.72 mmol) in CH_2Cl_2 (90 mL). The reaction mixture was stirred at −30 to −20 °C for 2 h, then methanol (2.1 mL) was added dropwise at 0 °C within 3 min, and stirring was continued at the same temperature for 15 min. A saturated aqueous NH_4Cl solution (8.4 mL) was then added, and the mixture was allowed to warm to 20 °C. After 45 min, the reaction mixture was diluted with Et_2O (80 mL), saturated aqueous potassium sodium tartrate (14 mL) was added and vigorous stirring was continued for an additional 1 h. The phases were separated, and the organic fraction was washed twice with a solution of citric acid (5.14 g, 26.72 mmol) in water (120 mL), with water (5 × 50 mL), brine (2 × 20 mL), dried, filtered and concentrated under reduced pressure. The residue was taken up with hexane (30 mL), filtered through a pad of Celite® and concentrated under reduced pressure to give the aldehyde **12** (9.0 g, 98% crude) as a colorless oil, which was used for the next step without further purification. R_f = 0.37 (EtOAc/hexane, 1:4). ^1H NMR (250 MHz, $CDCl_3$): δ = 0.03 [s, 6 H, $Si(CH_3)_2$], 0.86 [s, 9 H, $SiC(CH_3)_3$], 1.43 [s, 9 H, $C(CH_3)_3$], 1.78−2.20 (m, 1 H, 3-H_a), 2.22−2.41 (m, 1 H, 3-H_b), 2.78−3.12 (m, 1 H, 4-H), 3.45−4.02 (m, 5 H, 1-H, 2-H, 5-H), 9.63 (s, 1 H, CHO).

(2*S*,4*R*)-*N*-Boc-4-(*Z*)-Propenylprolinol (14): A freshly prepared 0.85 M solution of *t*BuOK in THF (108 mL, 91.8 mmol) was added to a suspension of ethyltriphenylphosponium bromide (44.00 g, 118.52 mmol) in THF (50 mL) at 0 °C. The cooling bath was removed, and stirring continued for an additional 2 h. The mixture was then cooled to −78 °C, and a solution of **12** (9.00 g, 26.20 mmol) in THF (30 mL) was added dropwise within 2 h. Stirring was continued at the same temperature for an additional 24 h, and then the mixture was allowed to warm to 20 °C for 24 h. After 48 h, the reaction flask was immersed in an ice-water bath, and a saturated aqueous solution of Na_2SO_4 (50 mL) was added. The reaction mixture was concentrated under reduced pressure, the residue was taken up with CH_2Cl_2/Et_2O, 1:4 (200 mL), filtered through a pad of silica gel (10 cm), concentrated, the residue was dissolved in Et_2O (20 mL), the solution was filtered, concentrated, the residue was dissolved in Et_2O/hexane, 1:1 (20 mL), the solution was filtered, concentrated, the residue was dissolved in hexane (20 mL), the solution was filtered, concentrated, the residue was dissolved in pentane (20 mL), the solution was filtered, concentrated, and the residue was finally purified by column chromatography (EtOAc/hexane, 1:8, R_f = 0.51) to give impure (2*S*,4*R*)-*N*-Boc-*O*-TBDMS-4-(*Z*)-propenylprolinol **13** (5.3 g) which was used for the next step without further purification.

TBAF·3H_2O (8.86 g, 28.1 mmol) was added with stirring to a solution of the crude alkene **13** (5.0 g, max. 14 mmol) in THF (15 mL)

at 20 °C. After 1.5 h, the mixture was taken up with Et_2O (100 mL), washed with water (5 × 20 mL), brine (2 × 20 mL), dried, concentrated under reduced pressure, and the residue was purified by column chromatography (EtOAc/hexane, 1:2.5, R_f = 0.32) to give **14** (2.69 g, 42% over 3 steps from **11**) as a colorless oil which solidified into a colorless solid upon seeding, and the (2*S*,4*S*)-epimer *epi*-**14** (0.12 g, 2%) as a colorless oil.

14: M.p. 41−43 °C, $[\alpha]_D^{20}$ = −47.9 (*c* = 0.97, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3398 cm^{-1}, 2976, 2932, 2871, 1696, 1402, 1164. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.23 (ddd, *J* = 10.8, 10.8, 10.8 Hz, 1 H, 3-H_a), 1.46 [s, 9 H, $C(CH_3)_3$], 1.65 (dd, *J* = 6.9, 0.8 Hz, 3 H, 3′-H), 2.13 (ddd, *J* = 10.8, 6.5, 6.5 Hz, 1 H, 3-H_b), 2.90 (ddd, *J* = 10.8, 10.8, 10.8 Hz, 1 H, 5-H_a), 2.85−3.10 (m, 1 H, 4-H), 3.52−3.77 (m, 3 H, 5-H_b, 2-H, 1-H_a), 3.96 (dd, *J* = 7.6, 14.9 Hz, 1 H, 1-H_b), 5.18 (m, 1 H, 1′-H), 5.30 (dd, *J* = 8.9, 1.8 Hz, 1 H, OH), 5.52 (dq, *J* = 9.8, 6.9 Hz, 1 H, 2′-H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.2 (+, CH_3), 28.4 [+, $C(CH_3)_3$], 35.2 (+, C-4), 35.8 (−, C-3), 52.7 (−, C-5), 61.1 (+, C-2), 67.6 (−, C-1), 80.4 [C_{quat}, $C(CH_3)_3$], 126.3 (+, C-2′), 129.8 (+, C-1′), 156.8 (C_{quat}, NCO_2). MS (EI): *m*/*z* (%) = 241 (1) [M^+], 210 (35) [$M^+ - CH_3O$], 168 (9), 154 (100) [$M^+ - C_5H_{11}O$], 110 (96) [$C_7H_{12}N^+$], 67 (5), 57 (89) [$C_4H_9^+$], 41 (15) [$C_3H_5^+$]. HRMS (EI): calcd. for $C_{13}H_{23}NO_3$: 241.1678; correct mass. Elemental analysis calcd. (%) for $C_{13}H_{23}NO_3$ (241.3): calcd. C 64.70, H 9.61, N 5.80; found C 64.83, H 9.74, N 5.64.

***epi*-14:** R_f = 0.28, EtOAc/hexane, 1:2.5. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.44 [s, 9 H, $C(CH_3)_3$], 1.60 (dd, *J* = 6.8, 1.8 Hz, 3 H, 3′-H), 1.68−1.85 (m, 2 H, 3-H), 3.01 (ddd, *J* = 9.7, 9.7, 9.7 Hz, 1 H, 5-H_a), 3.13 (m, 1 H, 4-H), 3.48 (dd, *J* = 9.7, 6.9 Hz, 1 H, 5-H_b), 3.54−3.59 (m, 2 H, 1-H_a, 2-H), 3.77−4.12 (m, 1 H, 1-H_b), 4.40 (br, 1 H, OH), 5.21 (dd, *J* = 10.9, 10.9 Hz, 1 H, 1′-H), 5.48 (dq, *J* = 10.9, 6.8 Hz, 1 H, 2′-H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.2 (+, CH_3), 28.4 [+, $C(CH_3)_3$], 34.8 (+, C-4), 35.1 (−, C-3), 52.7 (−, C-5), 59.6 (+, C-2), 67.7 (−, C-1), 80.2 [C_{quat}, $C(CH_3)_3$], 125.9 (+, C-2′), 130.4 (+, C-1′), 158.3 (C_{quat}, NCO_2).

(2*S*,4*R*)-*N*-Boc-4-(*Z*)-Propenylproline (15): A 2.67 M solution of Jones reagent (36.5 mL, 97.46 mmol) was added to a solution of alcohol **14** (2.35 g, 9.74 mmol) in acetone (800 mL) at 4 °C within 1 h, and the mixture was stirred at the same temperature for an additional 2 h. Isopropanol (5 mL) was then added dropwise within 10 min, and the mixture was allowed to warm to 20 °C. The reaction mixture was concentrated to 200 mL under reduced pressure at a bath temperature not higher than 30 °C, the residue was taken up with Et_2O (500 mL) and the mixture was washed with water (3 × 100 mL). The aqueous fraction was back-extracted with diethyl ether (3 × 50 mL), and the organic layers were combined, washed with brine (2 × 50 mL), dried, filtered, concentrated to 100 mL under reduced pressure, and the residue was extracted with saturated aqueous solution of $NaHCO_3$ (5 × 40 mL). The combined aqueous fractions were washed with Et_2O (2 × 50 mL), the pH of the aqueous fractions was carefully adjusted to 2.5−3 with solid $NaHSO_4$, the formed emulsion was extracted with Et_2O (2 × 100 mL) and the organic fraction was washed with 1 M $NaHSO_4$ (3 × 50 mL), water (3 × 50 mL), brine (2 × 20 mL), dried, filtered and concentrated under reduced pressure. The residue was recrystallized twice from hexane and finally purified by column chromatography [EtOAc/hexane, 1:3 (2% AcOH), R_f = 0.27] to give **15** (1.63 g, 65%) as a colorless solid. HPLC: detection: 200 nm, t_R = 18.58 min, gradient: 20 → 50% MeCN in H_2O (0.1% TFA) for 30 min, purity > 99%. M.p. 84−85 °C. $[\alpha]_D^{20}$ = −84.4 (*c* = 0.86, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3020, 2975, 2943, 2880, 2625, 1736, 1633, 1441, 1369, 1252, 1168. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.42, 1.48 [2 s, 9 H, $C(CH_3)_3$], 1.66 (d, *J* = 6.8 Hz, 3 H, 3′-H), 1.72−1.84, 1.93−2.12 (m, 1 H, 3-H_a), 2.27−2.54 (m, 1 H, 3-H_b), 3.06 (ddddd, *J* = 9.6, 9.6, 9.6, 9.6, 9.6 Hz, 1 H, 4-H), 2.98−3.20 (m, 1 H, 5-H_a), 3.64−3.86 (m, 1 H, 5-H_b), 4.25, 4.35 (2 dd, *J* = 8.3, 8.3 Hz, 1 H, 2-H), 5.26 (ddq, *J* = 9.6, 8.5, 1.8 Hz, 1 H, 1′-H), 5.52 (dq, *J* = 8.5, 6.8 Hz, 1 H, 2′-H), 10.30−11.40 (br, 1 H, CO_2H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.1 (+, CH_3), 28.1, 28.3 [+, $C(CH_3)_3$], 35.7, 36.1 (+, C-4), 36.1, 37.3 (−, C-3), 51.4, 51.9 (−, C-5), 58.9, 59.1 (+, C-2), 80.6 [C_{quat}, $C(CH_3)_3$], 126.6, 126.9 (+, C-2′), 129.0, 129.2 (+, C-1′), 153.6, 154.8 (C_{quat}, NCO_2), 177.3, 178.4 (C_{quat}, C-1). MS (ESI), positive *m*/*z* (%) = 300 (35) [$M - H^+ + 2Na^+$], 278 (16) [$M + Na^+$]; negative *m*/*z* = 254 (100) [$M - H^+$]. HRMS (EI): calcd. for $C_{13}H_{21}NO_4$: 255.1471; correct mass. Elemental analysis calcd. (%) for $C_{13}H_{21}NO_4$ (255.3): calcd. C 61.16, H 8.29, N 5.49; found C 61.16, H 8.23, N 5.31.

2-Acetamido-6-chloropyridine *N*-Oxide (17): *m*-Chloroperbenzoic acid (11.97 g, 90% purity, 62.44 mmol) was added to a solution of 2-acetamido-6-chloropyridine (**16**)[20] (8.24 g, 48.30 mmol) in CH_2Cl_2 (100 mL), and stirring was continued for an additional 60 h. K_2CO_3 (6.5 g) was then added to the mixture, and after stirring for 1 h the mixture was filtered, the solution was concentrated under reduced pressure, and the residue was recrystallized from CH_2Cl_2/hexane to give **17** (8.35 g, 93%) as a colorless solid. ^1H NMR (250 MHz, $CDCl_3$): δ = 2.29 (s, 3 H, CH_3), 7.15−7.31 (m, 2 H, 4-H, 5-H), 8.35 (dd, *J* = 2.5, 10.0 Hz, 1 H, 3-H), 9.80−10.20 (br, 1 H, NH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 25.0 (+, CH_3), 112.1 (+, C-3), 119.4 (+, C-5), 127.2 (+, C-4), 140.0 (C_{quat}, C-6), 145.4 (C_{quat}, C-2), 169.0 (C_{quat}, CH_3CO). MS (EI, 70 eV): *m*/*z* (%) = 188/186 (30/100) [M^+], 146/144 (30:100) [$M^+ - C_2H_2O$], 130/128 (3:8), 43 (78) [$C_2H_3O^+$]. HRMS (EI): calcd. for $C_7H_7ClN_2O_2$: 186.0196; correct mass.

***tert*-Butyl Acetyl(6-chloropyridin-2-yl)carbamate *N*-Oxide (18):** DMAP (0.54 g, 4.42 mmol) was added to a solution of **17** (8.35 g, 44.75 mmol) and Boc_2O (11.09 g, 50.81 mmol) in acetonitrile (60 mL), and stirring was continued for an additional 12 h. The reaction mixture was diluted with EtOAc (250 mL), washed with 1 M $NaHSO_4$ (3 × 40 mL), saturated aqueous $NaHCO_3$ (3 × 40 mL), H_2O (3 × 40 mL), brine (2 × 20 mL), dried, filtered and concentrated under reduced pressure. The crude product was recrystallized from EtOAc/hexane to give **18** (8.31 g, 65%) as a colorless solid which slowly decomposed at ambient temperature. R_f = 0.59 (EtOAc/hexane, 1:1). ^1H NMR (250 MHz, $CDCl_3$): δ = 1.35 [s, 9 H, $C(CH_3)_3$], 2.58 (s, 3 H, CH_3), 7.08−7.22 (m, 2 H, 3-H, 5-H), 7.41−7.49 (m, 1 H, 4-H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 25.5 (+, CH_3), 27.5 [+, $C(CH_3)_3$], 84.5 [C_{quat}, $C(CH_3)_3$], 124.0 (+, C-3), 124.5 (+, C-5), 125.8 (+, C-4), 141.9 (C_{quat}, C-6), 145.8 (C_{quat}, C-2), 150.0 (C_{quat}, NCO_2), 171.8 (C_{quat}, CH_3CO). MS (EI, 70 eV): *m*/*z* (%) = 288/286 (5:14) [M^+], 172/170 (30:100) [$M^+ - C_6H_{12}O_2$], 146/144 (30:90) [$M^+ - C_6H_{12}O_3$], 57 (93) [$C_4H_9^+$], 43 (32) [$C_2H_3O^+$]. HRMS (EI): calcd. for $C_{12}H_{15}ClN_2O_4$: 286.0720; correct mass.

2-(*tert*-Butyloxycarbonylamino)-6-chloropyridine *N*-Oxide (19): To a solution of **18** (8.31 g, 28.98 mmol) in methanol (70 mL) was added 1,1,3,3-tetramethylguanidine (4.53 mL, 36.10 mmol), and stirring was continued for an additional 40 min. The mixture was concentrated under reduced pressure to ca. 30 mL, the residue was diluted with Et_2O (100 mL), the mixture was washed with 1 M $NaHCO_3$ (2 × 20 mL), brine (2 × 20 mL), dried, filtered and concentrated under reduced pressure to leave a solid residue which was recrystallized from octane to give **19** (4.25 g, 60%) as a colorless solid. M.p. 103−105 °C. IR (KBr): $\tilde{\nu}$ = 3297 cm^{-1}, 3122, 2980, 1728, 1608, 1560, 1500, 1377, 1275, 1257, 1182, 1159. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.50 [s, 9 H, $C(CH_3)_3$], 7.09 (dd, *J* = 2.0,

8.3 Hz, 1 H, 3-H), 7.19 (dd, J = 8.3, 8.3 Hz, 1 H, 4-H), 8.06 (dd, J = 2.0, 8.3 Hz, 1 H, 5-H), 9.13−9.31 (br, 1 H, NH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 28.0 [+, C(CH_3)$_3$], 82.5 [C_{quat}, C(CH_3)$_3$], 110.6 (+, C-3), 118.2 (+, C-5), 126.9 (+, C-4), 140.0 (C_{quat}, C-6), 146.0 (C_{quat}, C-2), 151.2 (C_{quat}, NCO_2). MS (EI, 70 eV): m/z (%) = 246/244 (6:20) [M^+], 190/188 (3:8) [$M^+ - C_4H_8$], 173/171 (5:17) [$M^+ - C_4H_9O$], 146/144 (11:36) [$C_5H_5ClN_2O^+$], 57 (100) [$C_4H_9^+$], 41 (8). HRMS (EI): calcd. for $C_{10}H_{13}ClN_2O_3$: 244.0615; correct mass.

2-Amino-6-chloropyridine *N*-Oxide Hydrochloride (20·HCl): The *N*-Boc-protected amide **19** (4.22 g, 17.25 mmol) was deprotected by treatment with 3.9 M HCl in dioxane (100 mL) for 24 h. All volatiles were then removed and the residue was triturated with Et_2O to give **20**·HCl (3.03 g, 97%) as a colorless solid.

2-Amino-6-chloropyridine *N*-Oxide (20): 2,6-Dichloropyridine *N*-oxide (**21**)[21] (6.30 g, 38.4 mmol) was heated with 25% NH_3 in MeOH (100 mL) in a sealed tube at 105 °C for 26 h (TLC control). The tube was cooled in an ice-water bath, then opened, and the reaction mixture was filtered and concentrated under reduced pressure. The residue was dissolved in MeOH/$CHCl_3$, 1:4, the solution was filtered again and concentrated to give a dark-red oil, which was purified by column chromatography (MeOH/$CHCl_3$, 1:4, R_f = 0.50) and then by recrystallization ($CHCl_3$/hexane) to give **20** (3.04 g, 55%) as a colorless solid. R_f = 0.23 (EtOAc/hexane, 1:1); m.p. 133−135 °C. IR (KBr): $\tilde{\nu}$ = 3400−2500 cm^{-1}, 3192, 3147, 1653, 1628, 1550, 1502, 1412, 1216, 1188. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.03 (br, 2 H, NH_2), 6.31 (dd, J = 0.5, 7.9 Hz, 1 H, 3-H), 6.57 (dd, J = 0.5, 7.9 Hz, 1 H, 5-H), 7.29 (dd, J = 7.9, 7.9 Hz, 1 H, 4-H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 106.4 (+, C-3), 112.5 (+, C-5), 139.9 (+, C-4), 149.1 (C_{quat}, C-6), 158.7 (C_{quat}, C-2). MS (EI, 70 eV): m/z (%) = 146/144 (30:100) [M^+], 128/126 (10:30) [$M^+ - H_2O$], 119/117 (5:16) [M^+ − HCN], 109 (2) [M^+ − Cl], 100 (7), 99 (10), 92 (17), 93/91 (5:16), 81 (7). HRMS (EI): calcd. for $C_5H_5ClN_2O$: 144.0090; correct mass. Elemental analysis calcd. (%) for $C_5H_5ClN_2O$ (144.6): calcd. C 41.54, H 3.49, N 19.38; found C 41.41, H 3.54, N 19.46.

2-Azido-6-chloropyridine *N*-Oxide (22): A 2.5 M aqueous $NaNO_2$ (11.3 mL) was added dropwise to an ice-cold solution of 2-amino-6-chloropyridine *N*-oxide (**20**) (3.80 g, 26.3 mmol) in 85 mL of 10% HCl at such a rate that the internal temperature did not exceed 5 °C. The reaction mixture was stirred for an additional 10 min, then a 2.5 M NaN_3 solution (11.3 mL) was added dropwise at such a rate that the internal temperature did not exceed 5 °C, and stirring was continued at the same temperature for an additional 1 h. The reaction mixture was extracted with CH_2Cl_2 (8 × 50 mL), dried and filtered through a short column with silica gel eluting first with CH_2Cl_2 (1 L) and then with CH_2Cl_2/Et_2O, 1:1 (1 L). The combined fractions were concentrated to ca. 15 mL under reduced pressure and hexane (150 mL) was added. The precipitate was separated by filtration and washed with CH_2Cl_2/hexane, 1:10 to give after drying **22** (3.4 g, 76%) as a faint yellow solid. M.p. 83−88 °C (decomp.). IR (KBr): $\tilde{\nu}$ = 3126 cm^{-1}, 3077, 2130, 1597, 1470, 1390, 1212. ^{1}H NMR (250 MHz, $CDCl_3$): 6.84 (dd, J = 2.0, 8.3 Hz, 1 H, 3-H), 7.11 (dd, J = 8.3, 8.3 Hz, 1 H, 4-H), 7.24 (dd, J = 2.0, 8.6 Hz, 1 H, 5-H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 114.5 (+, C-3), 121.5 (+, C-5), 126.2 (+, C-4), 145.4 (C_{quat}, C-6), 156.8 (C_{quat}, C-2). MS (EI, 70 eV): m/z (%) = 172/170 (14:44) [M^+], 144/142 (5:16) [$M^+ - N_2$], 114/112 (18:56), 87/85 (6:18), 76 (100). HRMS (EI): calcd. for $C_5H_3ClN_4O$: 169.9995; correct mass. Elemental analysis calcd. (%) for $C_5H_3ClN_4O$ (170.6): calcd. C 35.21, H 1.77, N 32.85; found C 35.35, H 2.01, N 32.66.

5-Chloro-1-hydroxypyrrole-2-carbonitrile (23) and 5-Chloro-2-carbonitrile (24): A solution of 2-azido-6-chloropyridine *N*-oxide **22** (1.27 g, 7.45 mmol) in anhydrous benzene (32 mL) under argon was sealed in a thick-walled tube. The tube was heated first at 90 °C, then the temperature was allowed to increase to 105 °C, and the reaction mixture was left at this temperature for 15 min. Then the temperature was decreased to 85 °C, and stirring continued for an additional 4 h. After this, the reaction mixture was allowed to cool to 20 °C, and was concentrated under reduced pressure at a temperature not higher than 35 °C to give a red solid, which was purified by column chromatography (silica gel, EtOAc/hexane, 1:4) to give **23** (0.517 g, 49%, R_f = 0.37) as a light tan solid and **24** (0.12 g, 13%, R_f = 0.49) as a colorless solid.

23: R_f = 0.52 (EtOAc/hexane, 1:3); m.p. 101−102 °C. IR (KBr): $\tilde{\nu}$ = 3139 cm^{-1}, 3127, 3007, 2900, 2241, 1516, 1425, 1403, 1378. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.03 (d, J = 5.0 Hz, 1 H, 4-H), 6.67 (d, J = 5.0 Hz, 1 H, 3-H), 8.96 (br, 1 H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 100.5 (C_{quat}, C-2), 104.9 (+, C-4), 111.0 (C_{quat}, CN), 116.0 (+, C-3), 131.9 (C_{quat}, C-5). MS (EI, 70 eV): m/z (%) = 144/142 (30:100) [M^+], 127/125 (17:57) [M^+ − OH], 107 (2) [M^+ − Cl], 89 (3), 80 (49), 73 (9), 64 (26), 52 (9). HRMS (EI): calcd. for $C_5H_3ClN_2O$: 141.9934; correct mass. Elemental analysis calcd. (%) for $C_5H_3ClN_2O$ (142.5): calcd. C 42.13, H 2.12, N 19.65; found C 42.03, H 2.35, N 19.44.

24: R_f = 0.49 (EtOAc/hexane, 1:4), m.p. 104−105 °C. IR (KBr): $\tilde{\nu}$ = 3144 cm^{-1}, 3122, 3078, 2978, 22331, 1731, 1543, 1449, 1421, 1383, 1261, 1145, 1035. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.03 (d, J = 7.5 Hz, 1 H, 4-H), 6.67 (d, J = 7.5 Hz, 1 H, 3-H), 8.96 (bs, 1 H, NH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 100.0 (C_{quat}, C-2), 108.6 (+, C-4), 113.6 (C_{quat}, CN), 120.8 (C_{quat}, C-5), 121.5 (+, C-3). MS (EI, 70 eV): m/z (%) = 128/126 (30:100) [M^+], 101/99 (1:3) [M^+ − HCN], 91 (4) [M^+ − Cl], 77/75 (1:4), 64 (16). HRMS (EI): calcd. for $C_5H_3ClN_2$: 125.9985; correct mass.

5-Chloro-1-(methoxymethoxy)pyrrole-2-carbonitrile (25): To a vigorously stirred emulsion of a 24% aqueous NaOH solution (1.40 mL) in a solution of 5-chloro-1-hydroxypyrrole-2-carbonitrile (**23**) (0.65 g, 4.56 mmol) and TEBAC (0.07 g, 0.31 mmol) in CH_2Cl_2 (10 mL) was added MOMCl (0.74 g, 9.19 mmol), and vigorous stirring was continued for an additional 30 min. The organic layer was then separated, and the aqueous fraction was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were then concentrated under reduced pressure, and the crude product was purified first by column chromatography (EtOAc/hexane, 1:7) and finally by bulb-to-bulb distillation at a bath temperature 60−100 °C and a pressure of 0.02 Torr to give **25** (0.84 g, 98%) as a colorless liquid which solidified in a refrigerator to a colorless solid. R_f = 0.55 (EtOAc/hexane, 1:4). IR (film): $\tilde{\nu}$ = 3136 cm^{-1}, 2945, 2839, 2227, 1430, 1218, 1167, 1091. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.73 (s, 3 H, CH_3), 5.18 (s, 2 H, CH_2), 6.05 (d, J = 4.8 Hz, 1 H, 4-H), 6.65 (d, J = 4.8 Hz, 1 H, 3-H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 58.9 (+, CH_3), 102.1 (C_{quat}, C-2), 104.2 (−, CH_2), 105.1 (+, C-4), 111.6 (C_{quat}, CN), 115.5 (+, C-3), 118.6 (C_{quat}, C-5). MS (EI, 70 eV): m/z (%) = 188/186 (3:8) [M^+], 127/125 (2:5) [$M^+ - C_2H_5O_2$], 64 (3), 45 (100) [$C_2H_5O^+$]. HRMS (EI): calcd. for $C_7H_7ClN_2O_2$: 186.0196; correct mass. Elemental analysis calcd. (%) for $C_7H_7ClN_2O_2$ (186.6): calcd. C 45.06, H 3.78, N 15.01; found C 44.87, H 3.79, N 14.81.

5-Chloro-1-(methoxymethoxy)pyrrole-2-carboxamide (26): To a vigorously stirred solution of 5-chloro-1-(methoxymethoxy)pyrrole-2-carbonitrile (**25**) (0.84 g, 4.50 mmol) and tetra-*n*-butylammonium hydrogen sulfate (0.32 g, 0.94 mmol) in CH_2Cl_2 (9 mL) were added a 20% aqueous NaOH (2.00 mL) and 30% H_2O_2 (3.28 mL, 32.10 mmol), and vigorous stirring was continued for an additional 90 min. The layers were separated and the water layer after saturation with sodium chloride was additionally extracted with CH_2Cl_2 (4 × 5 mL). The combined organic layers were concentrated under reduced pressure and the residue was purified by column chromatography (EtOAc/hexanes, 1:1, R_f = 0.29) to give **26** (0.80 g, 87%) as a colorless solid. M.p. 43−45 °C. IR (film): $\tilde{\nu}$ = 3466 cm^{-1}, 3339, 3192, 2943, 2838, 1658, 1606, 1440, 1166, 1085. ^1H NMR (250 MHz, $CDCl_3$): δ = 3.55 (s, 3 H, CH_3), 5.25 (s, 2 H, CH_2), 5.50−6.50 (br, 2 H, NH_2), 6.05 (d, J = 4.8 Hz, 1 H, 4-H), 6.73 (d, J = 4.8 Hz, 1 H, 3-H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 59.5 (+, CH_3), 104.2 (+, C-4), 104.8 (−, CH_2), 111.4 (+, C-3), 118.6 (C_{quat}, C-2), 122.1 (C_{quat}, C-5), 160.4 (C_{quat}, $CONH_2$). MS (EI, 70 eV): *m*/*z* (%) = 206/204 (11:32) [M^+], 174/172 (23:70) [$M^+ - CH_4O$], 145:143 (4:13) [$M^+ - C_2H_5O_2$], 90:88 (2:6), 45 (100) [$C_2H_5O^+$]. HRMS (EI): calcd. for $C_7H_9ClN_2O_3$: 204.0302; correct mass. Elemental analysis calcd. (%) for $C_7H_9ClN_2O_3$ (204.6): calcd. C 41.09, H 4.43, N 13.69; found C 41.32, H 4.21, N 13.47.

Di-*tert*-butyl [5-Chloro-1-(methoxymethoxy)pyrrol-2-yl]carbonylimidodicarbamate (27) and *tert*-Butyl Bis[(5-chloro-1-(methoxymethoxy)pyrrol-2-yl)carbonyl]imidocarbamate (28): To a solution of 5-chloro-1-(methoxymethoxy)pyrrole-2-carboxamide (**26**) (0.80 g, 3.91 mmol) and Boc_2O (5.12 g, 23.46 mmol) in anhydrous MeCN (20 mL) was added 4-pyrrolidinopyridine (50 mg, 0.34 mmol), and stirring was continued for an additional 2.5 h. The mixture was concentrated under reduced pressure, and the crude product was purified by column chromatography (EtOAc/hexane, 1:8) to give the desired twofold *N*-Boc-substituted product **27** (1.324 g, 84%, R_f = 0.13) as a colorless solid and the by-product **28** (95 mg, 10%, R_f = 0.07) as a viscous opaque oil.

27: M.p. 67−68 °C. IR (KBr): $\tilde{\nu}$ = 3123 cm^{-1}, 3012, 2971, 2946, 1793, 1696, 1431, 1391, 1371, 1275, 1255, 1156, 1102. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.42 [s, 18 H, 2 × $C(CH_3)_3$], 3.68 (s, 3 H, CH_3), 5.22 (s, 2 H, CH_2), 6.07 (d, J = 4.9 Hz, 1 H, 4-H), 6.75 (d, J = 4.9 Hz, 1 H, 3-H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 27.7 [+, 2 × $C(CH_3)_3$], 58.8 (+, CH_3), 84.0 [C_{quat}, 2 × $C(CH_3)_3$], 104.5 (−, CH_2), 104.9 (+, C-4), 116.0 (+, C-3), 122.3 (C_{quat}, C-2), 124.2 (C_{quat}, C-5), 149.3 (C_{quat}, NCO_2), 157.0 (C_{quat}, CON). MS (EI, 70 eV): *m*/*z* (%) = 406:404 (2:6) [M^+], 350:348 (2:5) [$M^+ - C_4H_8$], 294:292 (2:6) [$M^+ - C_8H_{16}$], 250:248 (11:35) [$M^+ - C_9H_{16}O_2$], 190:188 (11:35), 174:172 (30:100) [$C_7H_7NO_2Cl^+$] 143 (31), 57 (100) [$C_4H_9^+$], 45 (58) [$C_2H_5O^+$]. HRMS (EI): calcd. for $C_{17}H_{25}ClN_2O_7$: 404.1350; correct mass. Elemental analysis calcd. (%) for $C_{17}H_{25}ClN_2O_7$ (404.9): calcd. C 50.44, H 6.22, N 6.92; found C 50.26, H 5.99, N 6.85.

28: IR (film): $\tilde{\nu}$ = 3131 cm^{-1}, 2979, 2940, 2946, 2840, 1751, 1700, 1429, 1395, 1370, 1256, 1149, 1087. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.39 [s, 9 H, $C(CH_3)_3$], 3.64 (s, 6 H, 2 × CH_3), 5.24 (s, 4 H, 2 × CH_2), 6.03 (d, J = 4.8 Hz, 2 H, 2 × 4-H), 6.74 (d, J = 4.8 Hz, 2 H, 2 × 3-H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 27.5 [+, $C(CH_3)_3$], 58.9 (+, 2 × CH_3), 84.5 [C_{quat}, $C(CH_3)_3$], 104.8 (−, 2 × CH_2), 104.8 (+, 2 × C-4), 115.2 (+, 2 × C-3), 122.5 (C_{quat}, 2 × C-2), 123.6 (C_{quat}, 2 × C-5), 151.1 (C_{quat}, NCO_2), 158.9 (C_{quat}, 2 × CON). MS (CI), *m*/*z* (%) = 513:512:511:510:509 (13:15:68:22:100) [$M + NH_4^+$], 496:495:494:493:492 (13:15:68:22:100) [$M + H^+$].

5-Chloro-1-(methoxymethoxy)pyrrole-2-carboxylic Acid (29): To a solution of the twofold *N*-Boc-substituted derivative **27** (1.320 g, 3.26 mmol) in dioxane (16 mL) was added 1 M NaOH solution (4.3 mL), and the mixture was stirred at 55 °C for 2 h. Then, all volatiles were removed under reduced pressure, the residue was taken up with H_2O (40 mL), and the resulting solution washed with CH_2Cl_2 (5 × 10 mL). The pH of the water layer was adjusted with 1 M $KHSO_4$ to 3, the aqueous phase saturated with sodium chloride, and the product was extracted with CH_2Cl_2 (4 × 20 mL). The organic phase was dried and concentrated to give after recrystallization from CH_2Cl_2/hexane the acid **29** (0.399 mg, 60%) as a colorless solid. R_f = 0.36 [EtOAc/hexane, 1:2.5 (5% AcOH)], m.p. 120−122 °C (decomp.). IR (KBr): $\tilde{\nu}$ = 3451 cm^{-1}, 3135, 3006, 2964, 2944, 2618, 2562, 1671, 1543, 1533, 1447, 1437, 1323, 1263, 1159, 1119. ^1H NMR (250 MHz, $CDCl_3$): δ = 3.71 (s, 3 H, CH_3), 5.25 (s, 2 H, CH_2), 6.06 (d, J = 4.9 Hz, 1 H, 4-H), 6.95 (d, J = 4.9 Hz, 1 H, 3-H), 9.8−12.2 (br, 1 H, CO_2H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 58.9 (+, CH_3), 104.6 (−, CH_2), 104.7 (+, C-4), 116.0 (+, C-3), 117.7 (C_{quat}, C-2), 122.8 (C_{quat}, C-5), 163.6 (C_{quat}, CO). MS (EI, 70 eV): *m*/*z* (%) = 207:205 (13:43) [M^+], 177:175 (2:5) [$M^+ - CH_2O$], 145:143 (2:7) [$M^+ - C_2H_6O_2$], 129 (7), 91:89 (2:6), 75:73 (1:3), 45 (100) [$C_2H_5O^+$]. HRMS (EI): calcd. for $C_7H_8ClNO_4$: 205.0142; correct mass. Elemental analysis calcd. (%) for $C_7H_8ClNO_4$ (205.6): calcd. C 40.89, H 3.92, N 6.81; found C 40.93, H 3.94, N 6.68.

***N*-Boc-3-(2*S*,1′*S*,2′*R*)-(*trans*-2′-Nitrocyclopropyl)alanine:** A solution of Boc_2O (0.500 g, 2.29 mmol) in acetone (2 mL) was added to a vigorously stirred solution of 3-(2*S*,1′*R*,2′*R*)-(*trans*-2′-nitrocyclopropyl)alanine (**30**) (0.266 g, 1.53 mmol) in 1 M NaOH (1.53 mL) with some $NaHCO_3$ (ca. 50 mg) (when a precipitate was formed, acetone and/or water were added to obtain a homogeneous solution), and stirring was continued for another 15 h. *N*,*N*-Dimethylaminopropylamine (0.11 mL, 0.88 mmol) was then added. After an additional 10 min, acetone was removed under reduced pressure, and the pH of the residual aqueous solution was adjusted to 2−3 with 1 M $NaHSO_4$ solution. The resulting emulsion was extracted with Et_2O (50 mL), and the ethereal layer was washed with 1 M $NaHSO_4$ solution (2 × 10 mL), water (3 × 10 mL), brine (2 × 5 mL), dried, filtered and concentrated under reduced pressure. The residue was taken up with hexane, filtered through a pad of Celite®, and concentrated under reduced pressure to give the title compound (0.353 g, 84%) as an extremely viscous colorless oil. R_f = 0.06 [EtOAc/hexane, 1:3 (2% AcOH)], $[\alpha]_D^{20}$ = 20.6 (c = 0.81, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3700−2250 cm^{-1}, 3101, 2979, 2935, 1715, 1545, 1437, 1394, 1369, 1253, 1163. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.14 (ddd, J = 6.5, 6.5, 6.5 Hz, 1 H, 3′-H_a), 1.45 [s, 9 H, $C(CH_3)_3$], 1.59−1.82 (m, 1 H, 3′-H_b), 1.82−1.94 (m, 1 H, 1′-H), 1.94−2.21 (m, 2 H, 3-H), 4.10−4.23 (m, 1 H, 2′-H), 4.25−4.38, 4.42−4.53 (2 m, 1 H, 2-H), 5.22−5.40, 6.10−7.30 (br, 2 H, NH, CO_2H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 17.5 (−, C-3′), 22.0 (+, C-1′), 28.1 [+, $C(CH_3)_3$], 33.4, 33.6 (−, C-3), 52.5, 53.7 (+, C-2), 59.2 (+, C-2′), 80.6, 82.5 [C_{quat}, $C(CH_3)_3$], 155.4, 156.9 (C_{quat}, NCO_2), 175.1, 175.4 (C_{quat}, C-1). MS (ESI): positive mode, *m*/*z* (%) = 319 (32) [$M - H^+ + 2Na^+$], 297 (86) [$M + Na^+$]; negative mode, *m*/*z* (%) = 273 (30) [$M - H^+$].

Boc-(*S*)-(3-Ncp)Ala-OFm (31): EDC (0.223 g, 1.16 mmol) was added to a cooled (4 °C) solution of Boc-(*S*)-(3-Ncp)Ala-OH (0.213 g, 0.78 mmol), 4-pyrrolidinopyridine (36 mg, 0.24 mmol) and 9-fluorenylmethanol (0.152 g, 0.78 mmol) in CH_2Cl_2 (6 mL). The temperature was allowed to reach 20 °C and stirring was continued for 5 h. The mixture was then diluted with Et_2O (50 mL) and subjected to the usual aqueous workup. The organic layer was

dried, filtered and concentrated under reduced pressure. The residue was crystallized from hexane, taken up with Et_2O (4 mL), and the solution was filtered through a silica gel pad (1.5 cm) to give, after concentration of the filtrate under reduced pressure, **31** (0.26 g, 74%) as a colorless solid. R_f = 0.30 (EtOAc/hexane, 1:4), m.p. 79−81 °C, $[\alpha]_D^{20}$ = −27.0 (c = 0.3, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3420 cm^{-1}, 3067, 2980, 2934, 1738, 1715, 1684, 1545, 1521, 1451, 1369, 1208, 1163. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.14 (ddd, J = 6.8, 6.8, 5.3 Hz, 1 H, 3′-H_a), 1.43 [s, 9 H, $C(CH_3)_3$], 1.43−1.60 (m, 1 H, 3′-H_b), 1.58−1.71 (m, 1 H, 1′-H), 1.72−1.92 (m, 2 H, 3-H), 3.90 (ddd, J = 6.9, 3.5, 3.5 Hz, 1 H, 2-H), 4.23 (t, J = 6.0 Hz, 1 H, 9′′′-H), 4.35 (ddd, J = 6.8, 6.8, 6.8 Hz, 1 H, 1′-H), 4.55 (dd, J = 10.8, 6.0 Hz, 1 H, 1′′-H_a), 4.66 (dd, J = 10.8, 6.0 Hz, 1 H, 1′′-H_b), 5.13 (d, J = 8 Hz, 1 H, NH), 7.26−7.48 (m, 4 H, Ar-H), 7.57 (d, J = 7.4 Hz, 2 H, Ar-H), 7.77 (d, J = 7.5 Hz, 2 H, Ar-H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 17.5 (−, C-3′), 21.8 (+, C-1′), 28.1 [+, $C(CH_3)_3$], 33.6 (−, C-3), 46.6 (+, C-1′′), 52.6 (+, C-2), 59.0 (+, C-2′), 66.9 (−,C-2′′), 80.2 [C_{quat}, $C(CH_3)_3$], 119.9, 120.0 (+, Ar-C), 124.6, 124.7 (+, Ar-C), 127.1 (+, Ar-C), 127.9 (+, Ar-C), 141.2, 141.3 (C_{quat}, Ar-C), 143.0, 143.2 (C_{quat}, Ar-C), 155.0 (C_{quat}, NCO_2), 175.4 (C_{quat}, C-1). MS (EI, 70 eV), m/z (%) = 452 (3) [M^+], 178 (100) [$C_{14}H_{10}^+$], 129 (2) [$C_5H_9N_2O_2^+$], 91 (3) [$C_7H_7^+$], 57 (16) [$C_4H_9^+$], 41 (5) [$C_3H_5^+$]. HRMS (EI): calcd. for $C_{25}H_{28}N_2O_6$: 452.1947; correct mass. Elemental analysis calcd. (%) for $C_{25}H_{28}N_2O_6$ (452.5): calcd. C 66.36, H 6.24, N 6.19; found C 66.11, H 5.99, N 6.02.

Chpca(MOM)-(2*S*)-(3-Ncp)Ala-OFm (32): The ester **31** (0.223 g, 0.49 mmol) was deprotected by treatment with 4 M HCl in EtOAc (5 mL) for 90 min to give HCl·H-(3-Ncp)Ala-OFm (0.182 g, 95%) as a colorless solid. EDC (93 mg, 0.49 mmol) and HOAt (64 mg, 0.47 mmol) were added to a cooled (4 °C) solution of **29** (96 mg, 0.47 mmol) in anhydrous CH_2Cl_2 (5 mL). After 5 min, to the solution of the amino ester were added DIEA (61 mg, 0.47 mmol) and TMP (0.114 g, 0.94 mmol) in anhydrous CH_2Cl_2 (1 mL). After 3 h, the reaction mixture was diluted with Et_2O (50 mL) and subjected to the usual aqueous workup. The organic layer was dried, filtered and concentrated under reduced pressure. The residue was crystallized from Et_2O/pentane to give **32** (0.202 g, 76% on two steps) as a colorless solid. R_f = 0.20 (EtOAc/hexane, 1:3), m.p. 94−95 °C, $[\alpha]_D^{20}$ = −33.3 (c = 0.3, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3370 cm^{-1}, 3038, 2962, 2935, 2836, 1729, 1638, 1538, 1428, 1374, 1339, 1239, 1164. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.14 [ddd, J = 6.8, 6.8, 5.5 Hz, 1 H, 3′-H_a, *(3-Ncp)Ala*], 1.47−1.60 [m, 1 H, 3′-H_b, *(3-Ncp)Ala*], 1.69−1.90 [m, 3 H, 1′-H, 3-H, *(3-Ncp)Ala*], 3.57 (s, 3 H, OMe), 3.89 [ddd, J = 7.0, 3.3, 3.3 Hz, 1 H, 2-H, *(3-Ncp)Ala*], 4.25 (t, J = 5.8 Hz, 1 H, 9′′-H, *Fm*), 4.63 (dd, J = 10.6, 5.8 Hz, 1 H, 1′-H_a, *Fm*), 4.73 (dd, J = 10.6, 5.8 Hz, 1 H, 1′-H_b, *Fm*), 5.17 (d, J = 6.8 Hz, 1 H, OCH_2O), 5.25 (d, J = 6.8 Hz, 1 H, OCH_2O), 6.04 (d, J = 4.7 Hz, 1 H, 4-H, *Chpca*), 6.68 (d, J = 4.7 Hz, 1 H, 3-H, *Chpca*), 7.17 (d, J = 7.0 Hz, 1 H, NH), 7.26−7.37 (m, 2 H, Ar-H, *Fm*), 7.42 (dd, J = 7.0, 7.0 Hz, 2 H, Ar-H, *Fm*), 7.57 (d, J = 7.3 Hz, 2 H, Ar-H, *Fm*), 7.77 (dd, J = 7.5, 3.6 Hz, 2 H, Ar-H, *Fm*); the signal of 1′-H_b of the Fm group overlapped with the signal of 1′-H of the (3-Ncp)Ala moiety. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 17.5 [−, C-3′, *(3-Ncp)Ala*], 21.7 [+, C-1′, *(3-Ncp)Ala*], 33.3 [−, C-3, *(3-Ncp)Ala*], 46.6 (+, C-9′′, *Fm*), 51.3 [+, C-2, *(3-Ncp)Ala*], 58.9 [+, C-2′, *(3-Ncp)Ala*], 59.4 (+, OMe), 66.9 (−, C-1′, *Fm*), 104.2 (+, C-4, *Chpca*), 104.8 (−, OCH_2O), 111.1 (+, C-3, *Chpca*), 118.7 (C_{quat}, C-2, *Chpca*), 119.9, 120.0 (+, Ar-C, *Fm*), 121.7 (C_{quat}, C-5, *Chpca*), 124.5, 124.6 (+, Ar-C, *Fm*), 127.1, 127.2 (+, Ar-C, *Fm*), 127.9 (+, Ar-C, *Fm*), 141.2, 141.3 (C_{quat}, Ar-C, *Fm*), 143.0, 143.1 (C_{quat}, Ar-C, *Fm*), 158.0 (C_{quat}, C-1, *Chpca*), 171.1 [C_{quat}, C-1, *(3-Ncp)Ala*]. MS (EI, 70 eV), m/z (%) = 541:539 (1:2) [M^+], 510:508 (1:3) [$M^+ - CH_3O$], 191 (10), 178 (100) [$C_{14}H_{10}^+$], 165 (12), 130:128 (3:10) [$C_5H_3ClNO^+$], 45 (36) [$C_2H_5O^+$]. HRMS (EI): calcd. for $C_{27}H_{26}ClN_3O_7$: 539.1459; correct mass. Elemental analysis calcd. (%) for $C_{27}H_{26}ClN_3O_7$ (540.0): calcd. C 60.06, H 4.85, N 7.78; found C 60.10, H 5.00, N 7.71.

Chpca-(2*S*)-(3-Ncp)Ala-OFm (33): $MgBr_2{\cdot}Et_2O$ (0.239 g, 0.93 mmol) and EtSH (0.07 mL, 0.95 mmol) were added to a vigorously stirred solution of the acylamino ester **32** (50 mg, 92.6 μmol) in CH_2Cl_2 (15 mL), and stirring was continued for another 3 h. The reaction mixture was then taken up with EtOAc (40 mL), and washed with 1 M $NaHSO_4$ solution (3 × 10 mL), water (3 × 5 mL), brine (2 × 5 mL), dried, filtered and concentrated under reduced pressure. The residue was purified by preparative TLC (200 × 200 mm, EtOAc/hexane, 1:4, 2 runs) and gave **33** (36 mg, 78%) as an extremely viscous oil which was unlimitedly stable upon storage under argon at −28 °C. R_f = 0.20 (EtOAc/hexane, 1:3). IR (KBr): $\tilde{\nu}$ = 3750−1800 cm^{-1}, 3067, 1740, 1542, 1451, 1426, 1368, 1198. ^1H NMR (250 MHz, $CDCl_3$): δ = 0.83−0.96 [m, 1 H, 3′-H_a, *(3-Ncp)Ala*], 1.42−1.56 [m, 1 H, 3′-H_b, *(3-Ncp)Ala*], 1.67−1.82 [m, 3 H, 1′-H, 3-H, *(3-Ncp)Ala*], 3.89 [ddd, J = 7.0, 3.1, 3.1 Hz, 1 H, 2-H, *(3-Ncp)Ala*], 4.25 (t, J = 5.1 Hz, 1 H, 9′′-H, *Fm*), 4.67 (dd, J = 10.7, 5.1 Hz, 1 H, 1′-H_a, *Fm*), 4.82 (dd, J = 10.7, 5.1 Hz, 1 H, 1′-H_b, *Fm*), 5.96 (d, J = 5.0 Hz, 1 H, 4-H, *Chpca*), 6.37 (d, J = 7.0 Hz, 1 H, NH), 6.40 (d, J = 5.0 Hz, 1 H, 3-H, *Chpca*), 7.26−7.37 (m, 2 H, Ar-H, *Fm*), 7.42 (dd, J = 7.3, 7.3 Hz, 2 H, Ar-H, *Fm*), 7.56 (d, J = 7.3 Hz, 2 H, Ar-H, *Fm*), 7.76 (dd, J = 7.1, 5.3 Hz, 2 H, Ar-H, *Fm*), 13.0−13.3 (br, 1 H, OH); the signal of 1′-H_a of the Fm group overlapped with the signal of 1′-H of the (3-Ncp)Ala moiety. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 17.4 [−, C-3′, *(3-Ncp)Ala*], 21.6 [+, C-1′, *(3-Ncp)Ala*], 33.4 [−, C-3, *(3-Ncp)Ala*], 46.7 (+, C-9′′, *Fm*), 51.2 [+, C-2, *(3-Ncp)Ala*], 58.9 [+, C-2′, *(3-Ncp)Ala*], 66.9 (−, C-1′, *Fm*), 102.8 (+, C-4, *Chpca*), 106.1 (+, C-3, *Chpca*), 114.4 (C_{quat}, C-2, *Chpca*), 116.0 (C_{quat}, C-5, *Chpca*), 120.0, 120.1 (+, Ar-C, *Fm*), 124.4, 124.5 (+, Ar-C, *Fm*), 127.2, 127.3 (+, Ar-C, *Fm*), 128.0 (+, Ar-C, *Fm*), 141.3, 141.4 (C_{quat}, Ar-C, *Fm*), 142.9, 143.0 (C_{quat}, Ar-C, *Fm*), 162.2 (C_{quat}, C-1, *Chpca*), 170.9 [C_{quat}, C-1, *(3-Ncp)Ala*]. MS (EI, 70 eV), m/z (%) = 497:495 (2:7) [M^+], 319:317 (1:4) [$M^+ - C_{14}H_{10}$], 178 (100) [$C_{14}H_{10}^+$], 146:144 (3:10) [$C_5H_2ClNO_2^+$]. HRMS (EI): calcd. for $C_{25}H_{22}ClN_3O_7$: 495.1197; correct mass.

Chpca-(2*S*)-(3-Ncp)Ala-OH (34): The ester **33** (35 mg, 70.6 μmol) was deprotected by treatment with 10% tris(2-aminoethyl)amine (TAEA) in CH_2Cl_2 (1 mL) for 20 min and the mixture was then taken up with EtOAc (30 mL). The organic layer was briefly washed with 1 M $NaHSO_4$ solution (3 × 10 mL), water (3 × 5 mL), brine (2 × 5 mL), dried, filtered and concentrated to give **34** as a turbid oil which completely polymerized into a colorless insoluble solid at 20 °C within ca. 2 h. In solution **34** was even less stable. ^1H NMR (250 MHz, [D_6]acetone): δ = 1.30 [ddd, J = 7.0, 7.0, 7.0 Hz, 1 H, 3′-H_a, *(3-Ncp)Ala*], 1.71−1.87 [m, 1 H, 3′-H_b, *(3-Ncp)Ala*], 1.90−2.21 [m, 3 H, 1′-H, 3-H, *(3-Ncp)Ala*], 4.42 [ddd, J = 6.3, 3.5, 3.5 Hz, 1 H, 2-H, *(3-Ncp)Ala*], 4.71−4.84 [m, 1 H, 2′-H, *(3-Ncp)Ala*], 6.03 (d, J = 5.0 Hz, 1 H, 4-H, *Chpca*), 6.82 (d, J = 5.0 Hz, 1 H, 3-H, *Chpca*), 7.0−8.0 (br, 2 H, OH, CO_2H), 8.17 (d, J = 7.5 Hz, 1 H, NH). It was impossible to obtain a ^{13}C NMR spectrum because **34** underwent complete decomposition during the measurement. MS (EI, 70 eV), m/z (%) = 319:317 (12:40) [M^+], 283 (6), 144 (100), 130:128 (15:46) [$C_5H_3ClNO^+$], 112 (6), 91:89 (4:12), 80 (18) [$C_5H_6N^+$], 64 (12), 45 (10) [CO_2H^+]. HRMS (EI): calcd. for $C_{11}H_{12}ClN_3O_6$: 317.0414; correct mass.

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