Combinatorial Solution-Phase Synthesis of (2*S*,4*S*)-4-Acylamino-5-oxopyrrolidine-2-carboxamides

Črt Malavašič,[†] Blaž Brulc,[†] Petra Čebašek,[†] Georg Dahmann,[‡] Niklas Heine,[‡] David Bevk,[†] Uroš Grošelj,[†] Anton Meden,[†] Branko Stanovnik,[†] and Jurij Svete*[,†]

Faculty of Chemistry and Chemical Technology, University of Ljubljana, Aškerčeva 5, P.O. Box 537, 1000 Ljubljana, Slovenia, and Department of Chemical Research, Boehringer Ingelheim Pharma GmbH & Co. KG, 88397 Biberach, Germany.

Received August 16, 2006

Solution-phase combinatorial synthesis of (2*S*,4*S*)-4-acylamino-5-oxopyrrolidine-2-carboxamides was studied. First, di-*tert*-butyl (2*S*,4*S*)-4-amino-5-oxopyrrolidine-1,2-dicarboxylate hydrochloride was prepared as the key intermediate in five steps from (*S*)-pyroglutamic acid. Acylation of the amino group followed by acidolytic deprotection gave (2*S*,4*S*)-4-acylamino-5-oxopyrrolidine-2-carboxylic acids, which were then coupled with amines to furnish a library of (2*S*,4*S*)-4-acylamino-5-oxopyrrolidine-2-carboxamides. Four coupling reagents, BPC, EEDQ, TBTU, and PFTU, were tested for the amidation reactions in the final step. Amidations with EEDQ and TBTU led to the desired carboxamides. On the other hand, BPC and PFTU were not suited, since diketopiperazines were sometimes obtained instead of the desired carboxamides.

Introduction

Because of their ability to mimic the structure of peptides and their ability to reverse binding to proteins, functionalized heterocycles are interesting scaffolds for the preparation of diversity-oriented compound libraries for medicinal and pharmaceutical applications.[1−8] In the past decades, various saturated monocyclic, fused, and spiro heterocycles with dipeptide or related structural motifs have been prepared and employed as conformationally constrained mimetics of dipeptides.[3,5−8] In this context, (*S*)-proline, (*S*)-pyroglutamic acid (**1**), and their derivatives play an important role as versatile starting materials and building blocks for the preparation of nonracemic saturated heterocycles, such as functionalized pyrrolidines, 5,5-, 5,6-, and 5,7-fused pyrrolidines, and spiro pyrrolidines containing a dipeptide or closely related structural motif.[8−14] So far, several pyrrolidine-containing libraries of biologically active compounds have been synthesized.[1−4,15−18]

However, there are not many reports on 4-aminopyroglutamic acid derivatives, despite the simplicity and interesting structural feature of their dipeptide-type structure.[19] Various 4-aminopyroglutamic acid derivatives have been prepared from L-glutamic acid,[20] L-pyroglutamic acid (**1**),[21,22] *trans*-4-hydroxy-L-proline,[23−25] and via Michael addition of acylaminomalonates[26,27] and azomethine ylides[28,29] to dehydroalanine esters.

2-Substituted alkyl 3-(dimethylamino)prop-2-enoates and related enaminones are a group of easily available enamino-masked alkyl α-formylacetates, which are versatile reagents in heterocyclic synthesis. They were used in the synthesis of various heterocyclic systems,[30−33] including functionalized heterocycles,[33−44] and natural product analogs.[33,45−49] Recently, the use of 3-(dimethylamino)prop-2-enoates was extended toward combinatorial synthesis of protected 3-(arylamino)alanines and fused heterocycles.[50−53] Until now, several reviews on utilization of 3-(dimethylamino)prop-2-enoates and analogous reagents in heterocyclic synthesis have been published.[30−37] In connection with the synthesis of γ-aminopyroglutamic acid derivatives, we have previously reported a stereoselective amination of chiral γ-lactams and γ-lactones.[21] The synthetic availability and interesting structural features of these α-amino lactams prompted us to carry out an extension toward the preparation of suitably protected γ-aminopyroglutamic acid derivatives as building blocks and scaffolds in combinatorial synthesis of (2*S*,4*S*)-4-acylamino-5-oxopyrrolidine-2-carboxamides as potential peptidomimetics.

Herein, we report the first results of this study: (a) a five-step synthesis of 1,2-di-*tert*-butyl (2*S*,4*S*)-4-amino-5-oxopyrrolidine-1,2-dicarboxylate (**6**) hydrochloride from (*S*)-pyroglutamic acid (**1**) and (b) utilization of **6** as the key intermediate in combinatorial solution-phase synthesis of (2*S*,4*S*)-4-acylamino-5-oxopyrrolidine-2-carboxamides **11**.

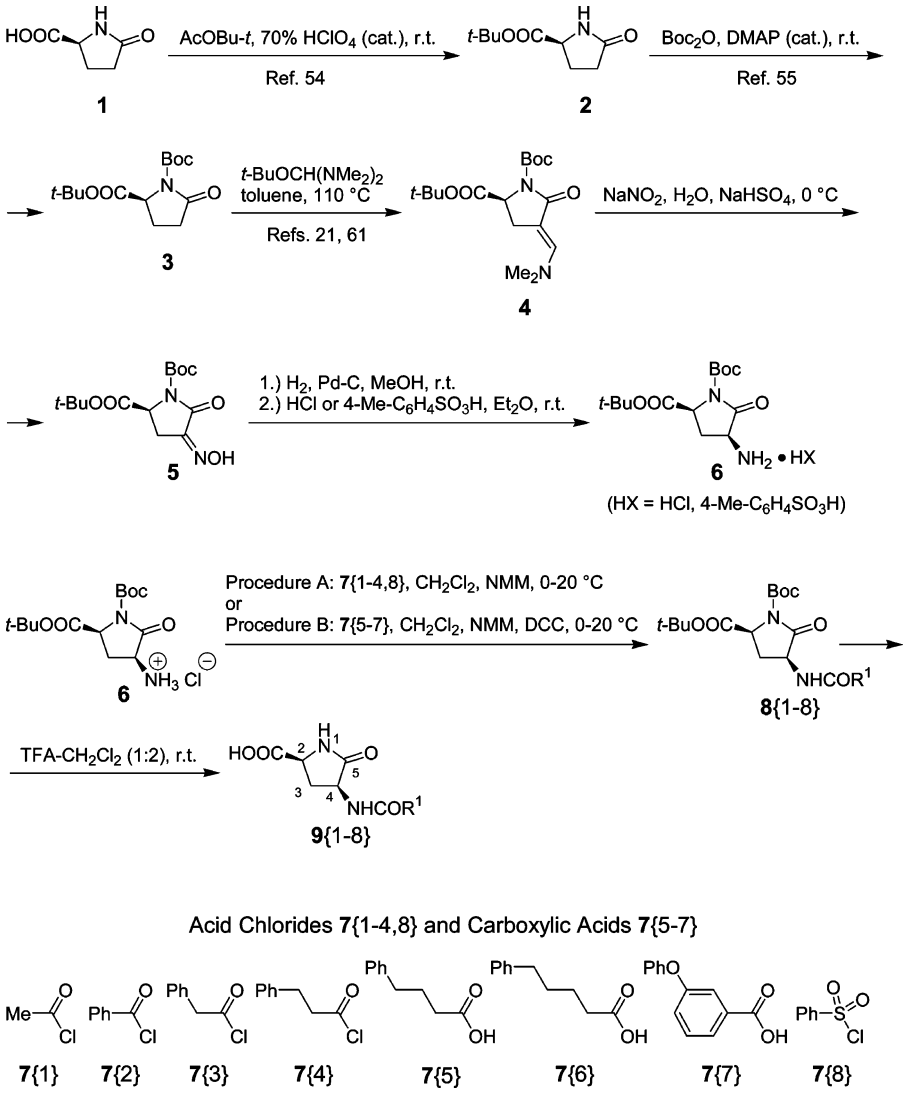
Results and Discussion

Preparation of 1,2-di-*tert*-Butyl (2*S*,4*S*)-4-Amino-5-oxopyrrolidine-1,2-dicarboxylate (6) and (2*S*,4*S*)-4-Acylamino-5-oxopyrrolidine-2-carboxylic Acids 9. First, 1,2-di-*tert*-butyl (*S*)-5-oxopyrrolidine-1,2-dicarboxylate (**3**) was prepared in two steps from (*S*)-pyroglutamic acid (**1**) following slightly modified literature procedures.[54,55] According to the previously published general stereoselective α-amination protocol,[21] γ-lactam **3** was then transformed in three steps into 1,2-di-*tert*-butyl (2*S*,4*S*)-4-amino-5-oxopy-

* Corresponding author. Phone: +386 1 2419 100. Fax: +386 1 2419 220. E-mail: jurij.svete@fkkt.uni-lj.si.
[†] University of Ljubljana.
[‡] Boehringer Ingelheim Pharma GmbH & Co. KG.

10.1021/cc060114s CCC: $37.00
Published on Web 12/22/2006

Scheme 1. Preparation of (2*S*,4*S*)-4-Acylamino-5-oxopyrrolidine-2-carboxylic Acids **9**{*1*−*8*}



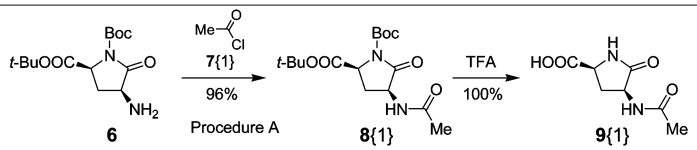
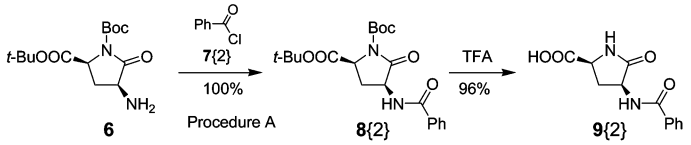
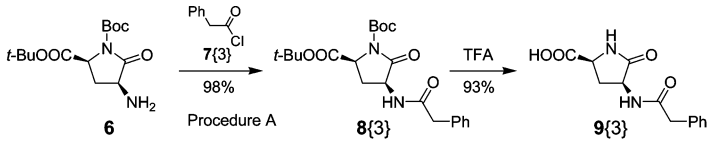
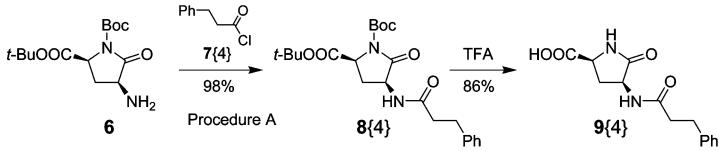
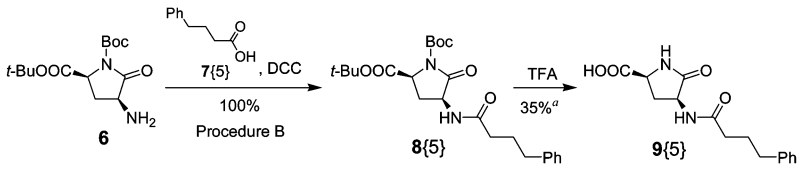
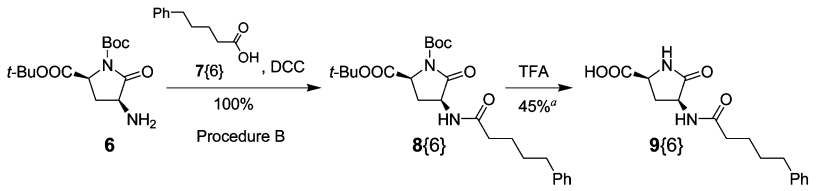
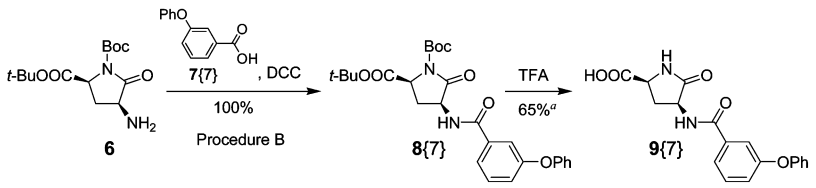
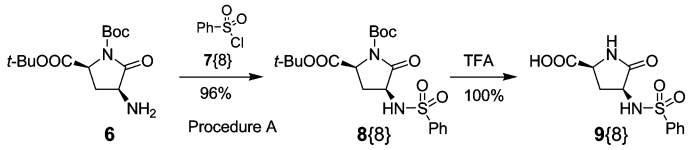
rrolidine-1,2-dicarboxylate **6**,[23] which was obtained in 82% de and in 91% yield over three steps. The crude, oily, free amine **6** was then treated with HCl−Et_2O or with *p*-toluenesulfonic acid in Et_2O to give the corresponding crystalline salts. Amine **6** hydrochloride was obtained in 68% yield and 100% de, whereas amine **6** 4-toluenesulfonate was obtained in 67% yield and 82% de. Because of the higher yield and isomeric purity, the hydrochloride of **6** was used as the key reagent for further transformations (Scheme 1).

Amine **6** hydrochloride was then N-acylated with acid chlorides **7**{*1*−*4*,*8*} and carboxylic acids **7**{*5*−*7*} to give the intermediates **8**{*1*−*8*}, which were subsequently deprotected with CH_2Cl_2−TFA to afford eight different (2*S*,4*S*)-4-acylamino-5-oxopyrrolidine-2-carboxylic acids **9**{*1*−*8*}. With respect to the N-acylation step, two procedures were employed: (a) acylation of the amine **6** hydrochloride with acid chlorides **7**{*1*−*4*,*8*} (procedure A) and (b) coupling of the amine **6** hydrochloride with carboxylic acids **7**{*5*−*7*} in the presence of DCC (procedure B) (Scheme 1, Table 1).

Once we had the desired (2*S*,4*S*)-4-acylamino-5-oxopyrrolidine-2-carboxylic acids **9**{*1*−*8*} in our hands, we studied parallel solution-phase couplings of the acids **9**{*1*−*8*} with amines **10**{*1*−*6*}. Four reagents were chosen for the activation of carboxylic acids **9**: (a) bis(pentafluorophenyl)-carbonate (BPC)[56−60] or *O*-pentafluorophenyl-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (PFTU),[61] giving pentafluorophenyl esters **12** as the reactive intermediates (method A); (b) 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ), giving mixed carbonic anhydrides **13** as the reactive intermediates (method B); and (c) *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(benzotriazol-1-yl)uronium tetrafluoroborate (TBTU), giving benzotriazol-1-yl esters **14** as the reactive intermediates (method C). Our intention was to prepare a small library of (2*S*,4*S*)-4-acylamino-5-oxopyrrolidine-2-carboxamides **11** and to find the most appropriate activation agent in terms of conversion, selectivity, and isolation of the final products (Scheme 2).

For efficient syntheses of larger combinatorial libraries, we were especially interested in identifying a coupling reagent that would allow for an amidation process with a minimized load of byproducts. During initial studies, we found that reagents yielding Pfp esters were very useful because the pentafluorophenol generated in the amidation process is volatile enough (literature[62] bp 143 °C at 751 Torr) to be eliminated by a simple evaporative workup procedure

Table 1. (2*S*,4*S*)-4-Amino-5-oxopyrrolidine-2-carboxylic Acid Derivatives **8** and **9**

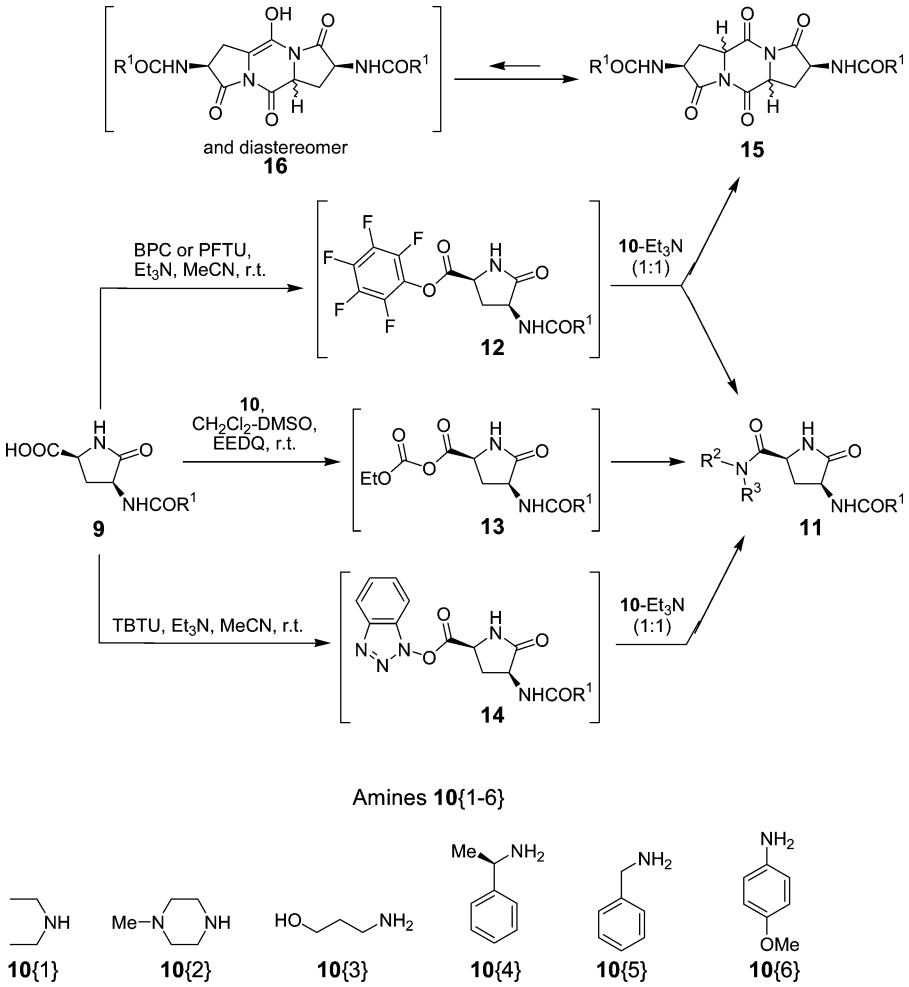
Compound	Reaction Conditions, Procedure, Yield
8{1}, **9**{1}	
8{2}, **9**{2}	
8{3}, **9**{3}	
8{4}, **9**{4}	
8{5}, **9**{5}	
8{6}, **9**{6}	
8{7}, **9**{7}	
8{8}, **9**{8}	

[a] Upon crystallization from water.

in a vacuum centrifuge at elevated temperatures (60 °C).[63] For example, BPC yields pentafluorophenol and CO_2 as byproducts and was found to be a very interesting alternative to classical coupling reagents, such as TBTU. We also found PFTU to be interesting, because the additional byproduct *N*,*N*,*N*′,*N*′-tetramethylurea (literature[64] bp = 175 °C at 740 Torr) can be evaporated, as well.[63] In addition, Carroll et al. have previously shown that EEDQ can be used as a coupling reagent in an evaporative workup protocol because it liberates ethanol, CO_2, and quinoline.[65] DCC was not investigated as a potential coupling reagent, because separation of the less soluble amidation products from the nonvolatile *N*,*N*′-dicyclohexylurea (DCU) as the byproduct would most probably be problematic.

Solution-Phase Synthesis of Carboxamides 11 by Activation of the Acids 9 with BPC or PFTU (Method A). The acids **9** were first treated with 1 equiv of triethylamine in acetonitrile, followed by addition of BPC or PFTU to give the intermediate pentafluorophenyl esters **12**. The in-situ-formed active esters **12** were subsequently treated with a mixture of amine **10** and triethylamine in a ratio of 1:1, respectively, to furnish the amidation products. To our

Scheme 2



surprise, the outcome of these amidations was rather unpredictable, since two types of products were obtained: carboxamides **11** and diketopiperazines **15**. The outcome of the amidation reaction was dependent on the type of amine employed. Thus, amidations of **9**{*1*−*6*} with primary aliphatic amines **10**{*3*−*5*} afforded carboxamides **11**, whereas amidations of **9**{*2*−*5*} with secondary amines **10**{*1,2*} and *p*-anisidine (**10**{*6*}) gave diketopiperazines **15**{*2*−*5*} or mixtures of **11** and **15** as products. Acetonitrile-soluble compounds **11**{*2*;*1,2*}, **11**{*3*;*1,3,4*}, and **15**{*3*} (or mixtures of **11** and **15**) were isolated by evaporation in vacuo in purities below 80% and were characterized only by ^{1}H NMR. Since we were primarily interested in a simple workup, no attempts were made toward additional purification of these final products **11** and **15** (procedure A). On the other hand, compounds **11**{*1*;*4,6*}, **11**{*2*;*3,4*}, **11**{*4*;*5*}, **11**{*5*;*3*−*5*}, **11**{*6*;*3,4*}, and **15**{*2,4,5*} were formed as precipitates and were isolated by filtration, washing, and drying in 28−100% yields and in >86% purity and were fully characterized (procedure B). Amides **11**{*1*;*4,6*}, **11**{*5*;*3*−*5*}, and **11**{*6*;*3*} and diketopiperazines **15**{*4,5*} were obtained in analytically pure form (Scheme 2, Table 2).

Apparently, two competitive reactions took place in amidations of carboxylic acids **9** using BPC or PFTU as activating reagent: (a) amidation, leading to the carboxamide **11**, or (b) dimerization of **9**, leading to the diketopiperazine **15**. This lack of selectivity could be attributed to steric as well as electronic factors. In the case of sterically unhindered primary aliphatic amines **10**{*3*−*5*}, amidation is faster than dimerization, and vice versa, more hindered and more basic secondary aliphatic amines **10**{*1,2*} favor the dimerization process. On the other hand, *p*-anisidine **10**{*6*} is less basic and less nucleophilic than aliphatic amines. Diminished nucleophilicity is then reflected in competition between amidation and dimerization. The formation of diketopiperazines **15** was not expected under the very mild amidation conditions, yet explainable. Namely, the pyroglutamic diketopiperazine (pyroglutamic anhydride) known in the literature is prepared by cyclodehydration of pyroglutamic acid with acetic anhydride−pyridine[66,67] or by cyclocondensation of pyroglutamic chloride.[68] In addition, a closely related dimerization/epimerization reaction has been reported recently for the pentafluorophenyl (*S*)-pyroglutamate as reactive intermediate in the peptide synthesis.[69] In most cases, ^{1}H NMR spectra of pure diketopiperazines **15**{*2,4,5*} exhibited three sets of signals. These sets of signals can be explained by base-promoted epimerization of the initially formed 2*S*,5a*S*,7*S*,10a*S* isomer **15** at positions 5a and 10a via the tautomeric form **16** (cf. Scheme 2). Since the 2*S*,5a*R*,7*S*,10a*S* isomer is identical to the 2*S*,5a*S*,7*S*,10a*R* isomer due to a C_2 symmetry axis, epimerization at positions 5a and 10a leads to three diastereomers.

Parallel Solution-Phase Synthesis of Carboxamides 11 by Activation of the Acids 9 with EEDQ (Method B). To

Table 2. Library of Carboxamides **11** and Diketopiperazines **15** Obtained by Method A

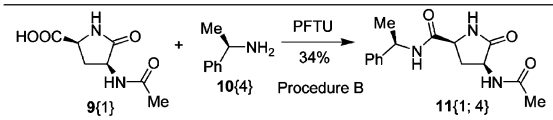
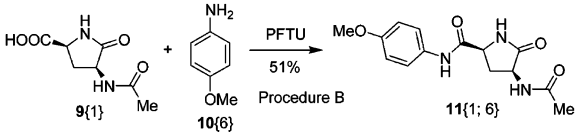
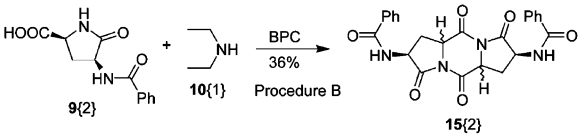
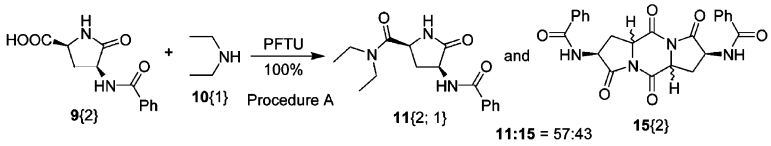
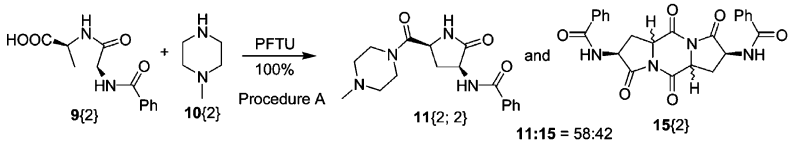
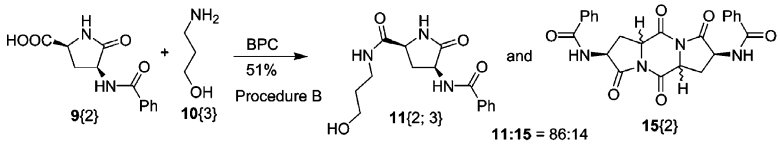
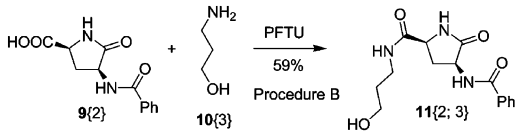
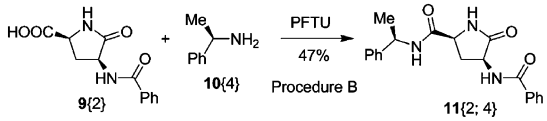
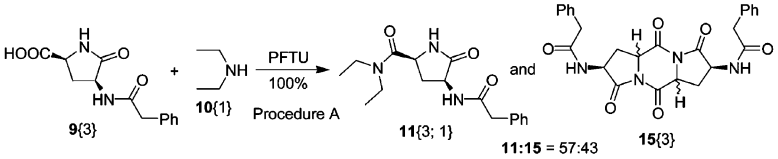
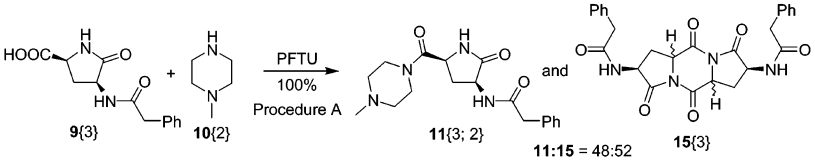
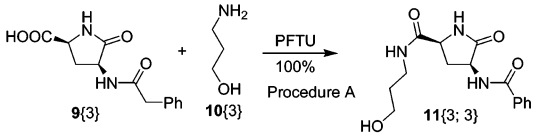
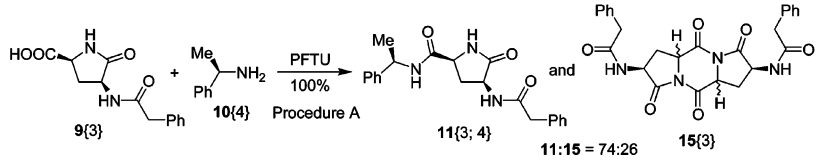
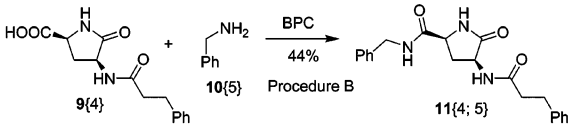
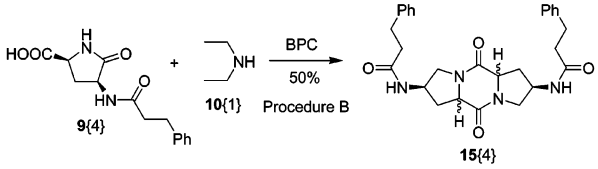
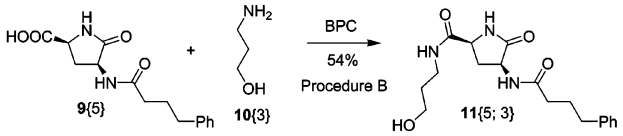
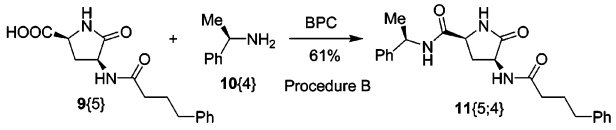
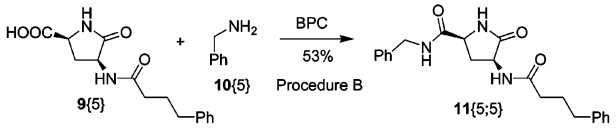
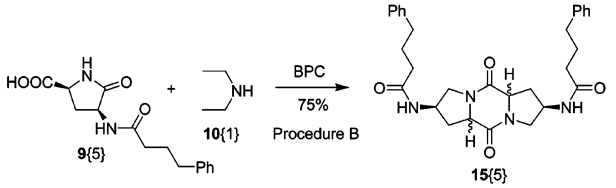
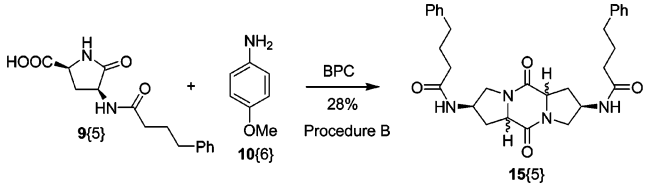
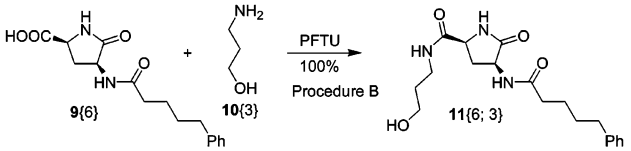
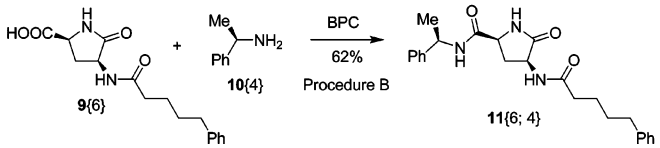
Reaction Conditions, Procedure, Yield	Purity[a] (%)
 **9**{1} **10**{4} PFTU, 34%, Procedure B → **11**{1; 4}	≥95[b]
 **9**{1} **10**{6} PFTU, 51%, Procedure B → **11**{1; 6}	≥95[b]
 **9**{2} **10**{1} BPC, 36%, Procedure B → **15**{2}	≥90[c]
 **9**{2} **10**{1} PFTU, 100%, Procedure A → **11**{2; 1} and **15**{2} **11:15** = 57:43	[d]
 **9**{2} **10**{2} PFTU, 100%, Procedure A → **11**{2; 2} and **15**{2} **11:15** = 58:42	[d]
 **9**{2} **10**{3} BPC, 51%, Procedure B → **11**{2; 3} and **15**{2} **11:15** = 86:14	86
 **9**{2} **10**{3} PFTU, 59%, Procedure B → **11**{2; 3}	≥90
 **9**{2} **10**{4} PFTU, 47%, Procedure B → **11**{2; 4}	≥90
 **9**{3} **10**{1} PFTU, 100%, Procedure A → **11**{3; 1} and **15**{3} **11:15** = 57:43	[d]
 **9**{3} **10**{2} PFTU, 100%, Procedure A → **11**{3; 2} and **15**{3} **11:15** = 48:52	[c, d]
 **9**{3} **10**{3} PFTU, 100%, Procedure A → **11**{3; 3}	30
 **9**{3} **10**{4} PFTU, 100%, Procedure A → **11**{3; 4} and **15**{3} **11:15** = 74:26	[d]

Table 2. (Continued)

Reaction Conditions, Procedure, Yield	Purity[a] (%)
 **9**{4} + **10**{5}; BPC, 44%, Procedure B → **11**{4; 5}	≥90
 **9**{4} + **10**{1}; BPC, 50%, Procedure B → **15**{4}	≥95[b,c]
 **9**{5} + **10**{3}; BPC, 54%, Procedure B → **11**{5; 3}	≥95[b]
 **9**{5} + **10**{4}; BPC, 61%, Procedure B → **11**{5;4}	≥95[b]
 **9**{5} + **10**{5}; BPC, 53%, Procedure B → **11**{5;5}	≥95[b]
 **9**{5} + **10**{1}; BPC, 75%, Procedure B → **15**{5}	≥95[b,c]
 **9**{5} + **10**{6}; BPC, 28%, Procedure B → **15**{5}	≥95[b]
 **9**{6} + **10**{3}; PFTU, 100%, Procedure B → **11**{6; 3}	≥95[b]
 **9**{6} + **10**{4}; BPC, 62%, Procedure B → **11**{6; 4}	≥90[e]

[a] Determined by ^{1}H NMR. [b] CHN analysis with the found values within ±0.4% deviation from theoretical values. [c] The product **15** was obtained as a mixture of three epimers. [d] The crude mixture of products **11** and **15** obtained upon evaporation was characterized only by NMR. No further separation and purification attempts were undertaken. [e] CHN analysis with the found values within ±0.5% deviation from theoretical values.

circumvent the side reaction observed in amidations with BPC and PFTU, we have chosen EEDQ as the next reagent for the activation of carboxylic acids **9**. Coupling with EEDQ does not require the presence of an additional equivalent of a tertiary base, thus diminishing the probability for the undesired dimerization reaction. Indeed, parallel treatment of equimolar mixtures of acids **9**{*1*−*5*,*7*} and amines **10**{*1*−*6*} with EEDQ in dichloromethane or dichloromethane−

Table 3. Library of Carboxamides **11** Prepared by Methods B and C

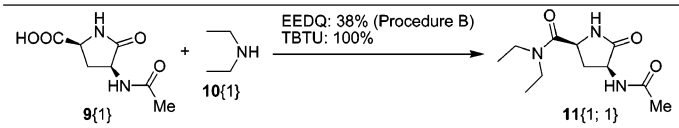
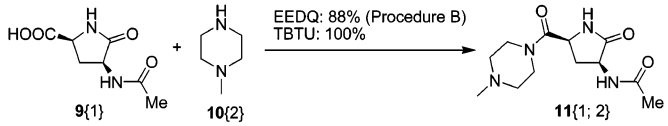
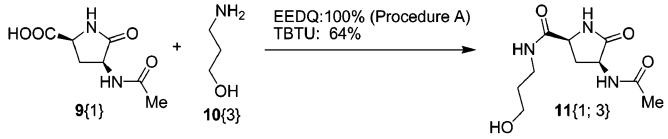
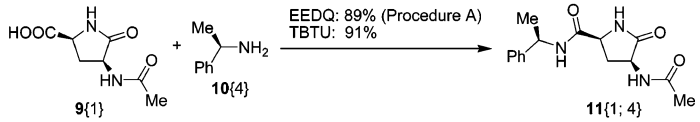
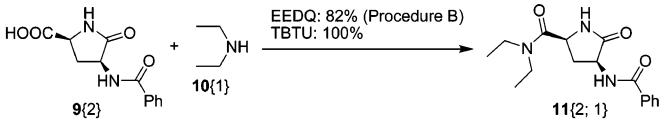
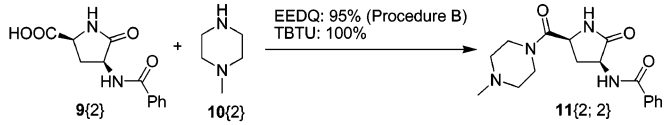
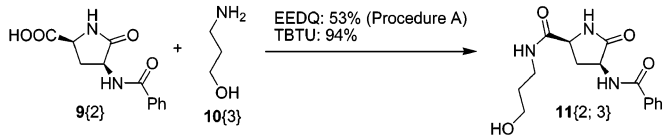
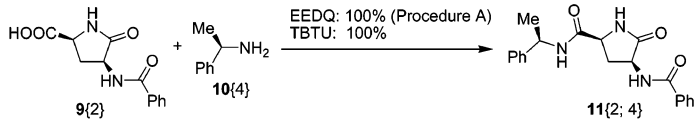
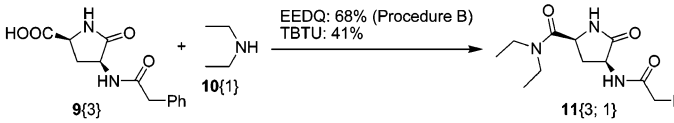
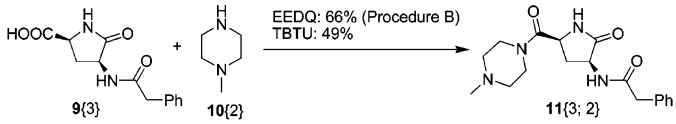
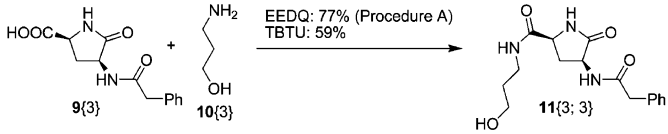
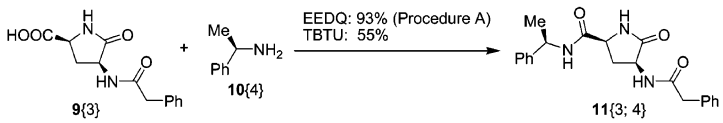
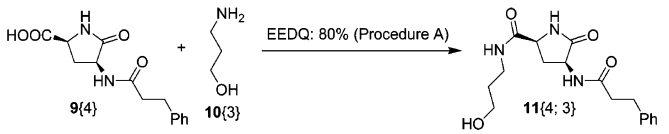
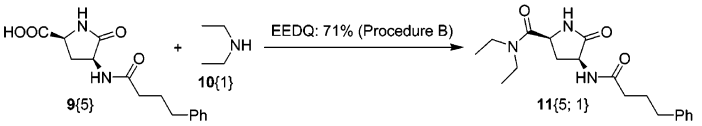
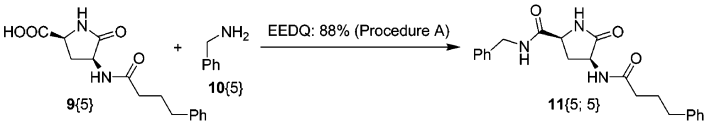
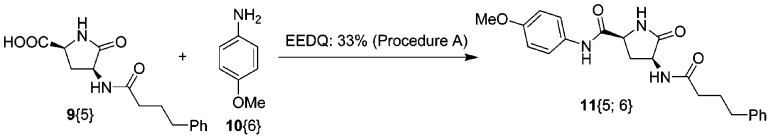
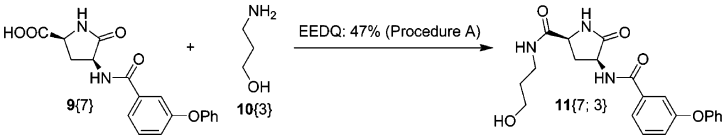
Reagents, Procedure, Yield	Purity (%)[a]	
	Method B (EEDQ)	Method C (TBTU)
 **9**{1} + **10**{1}; EEDQ: 38% (Procedure B) TBTU: 100%; **11**{1; 1}	≥95[b]	43
 **9**{1} + **10**{2}; EEDQ: 88% (Procedure B) TBTU: 100%; **11**{1; 2}	≥90	42
 **9**{1} + **10**{3}; EEDQ:100% (Procedure A) TBTU: 64%; **11**{1; 3}	49	48
 **9**{1} + **10**{4}; EEDQ: 89% (Procedure A) TBTU: 91%; **11**{1; 4}	≥95[b]	88
 **9**{2} + **10**{1}; EEDQ: 82% (Procedure B) TBTU: 100%; **11**{2; 1}	≥90	≥90
 **9**{2} + **10**{2}; EEDQ: 95% (Procedure B) TBTU: 100%; **11**{2; 2}	≥95[b]	≥90
 **9**{2} + **10**{3}; EEDQ: 53% (Procedure A) TBTU: 94%; **11**{2; 3}	≥95[b]	50
 **9**{2} + **10**{4}; EEDQ: 100% (Procedure A) TBTU: 100%; **11**{2; 4}	≥95[b]	≥90
 **9**{3} + **10**{1}; EEDQ: 68% (Procedure B) TBTU: 41%; **11**{3; 1}	≥95[b]	59
 **9**{3} + **10**{2}; EEDQ: 66% (Procedure B) TBTU: 49%; **11**{3; 2}	≥90[c]	≥90
 **9**{3} + **10**{3}; EEDQ: 77% (Procedure A) TBTU: 59%; **11**{3; 3}	≥95[b]	64
 **9**{3} + **10**{4}; EEDQ: 93% (Procedure A) TBTU: 55%; **11**{3; 4}	≥95[b]	89

Table 3. (Continued)

Reagents, Procedure, Yield	Purity (%)[a]	
	Method B (EEDQ)	Method C (TBTU)
 **9**{4} **10**{3} EEDQ: 80% (Procedure A) **11**{4; 3}	≥95[b]	
 **9**{5} **10**{1} EEDQ: 71% (Procedure B) **11**{5; 1}	≥90	
 **9**{5} **10**{5} EEDQ: 88% (Procedure A) **11**{5; 5}	≥95[b]	
 **9**{5} **10**{6} EEDQ: 33% (Procedure A) **11**{5; 6}	≥95[b]	
 **9**{7} **10**{3} EEDQ: 47% (Procedure A) **11**{7; 3}	≥95[b]	

[a] Determined by ^{1}H NMR. [b] CHN analysis with the found values within ±0.4% deviation from theoretical values. [c] CHN analysis with the found values within ±0.5% deviation from theoretical values.

DMSO (9:1) furnished the desired carboxamides **11** exclusively and without noticeable dimerization. A library of 17 carboxamides **11**{*1*−*3*;*1*−*4*}, **11**{*4*;*3*}, **11**{*5*;*1*,*5*,*6*}, and **11**{*7*;*3*} was synthesized in 33−100% yields and in >90% purity. Twelve amides **11** were obtained in analytically pure form. The less soluble amides **11**{*1*−*3*;*3*,*4*}, **11**{*4*;*3*}, **11**{*5*;*5*,*6*}, and **11**{*7*;*3*} precipitated from the reaction mixtures and were isolated by filtration, washing, and drying (procedure A). The dichloromethane-soluble compounds **11**{*1*−*3*;*1*,*2*} and **11**{*5*;*1*} were isolated by evaporation, filtration through basic aluminum oxide, and repeated evaporation (procedure B). An exception was carboxamide **11**{*1*;*3*}, which was obtained as a gummy precipitate and was isolated in 49% purity upon evaporative workup (Scheme 2, Table 3).

Parallel Solution-Phase Synthesis of Carboxamides 11 by Activation of the Acids 9 with TBTU (Method C). Finally, amidations of **9**{*1*−*3*} were carried out with amines **10**{*1*−*4*} using TBTU as the activating reagent. The acids **9**{*1*−*3*} were first transformed in situ with TBTU in the presence of 1 equiv of triethylamine into the corresponding HOBt esters **14**{*1*−*3*}, which were then treated with amines **10**{*1*−*4*} in the presence of 1 equiv of triethylamine. Evaporation of the reaction mixtures, removal of HOBt by filtration through basic aluminum oxide, and repeated evaporation of the filtrates furnished carboxamides **11**{*1*−*3*;*1*−*4*}. In this manner, a library of 12 carboxamides **11**{*1*−*3*;*1*−*4*} was obtained in 41−100% yields and in 42−90% purity. Despite the fact that these amidation conditions were similar to conditions employed in method A, formation of diketopiperazines **15** was not observed. From this point of view, method C was comparable to method B; however, the average purity of the products was lower (Scheme 2, Table 3).

All novel compounds **5**, **6**, **8**, **9**, **11**, and **15** were characterized by spectroscopic (IR, EI-MS, EI-HRMS, ^{1}H and ^{13}C NMR) methods and by elemental analyses for C, H, and N. Pure compounds **8**{*1*,*3*}, **11**{*1*;*2*}, **11**{*2*;*1*}, **11**{*3*;*2*}, **11**{*4*;*5*}, **11**{*5*;*1*}, **11**{*6*;*4*}, and **15**{*2*} were not prepared in analytically pure form. Their structures were confirmed by MS and HRMS. Compounds **8**{*5*−*7*} were isolated as the crude oily intermediates and were used for further transformations without characterization and purification. The purities of all compounds **11** and **15** were first determined by ^{1}H NMR. Compounds exhibiting ≥90% purity according to ^{1}H NMR were further evaluated by elemental analyses for C, H, and N. The relative configurations at positions 2 and 4 in the major 2*S*,4*S* isomer **6** and the minor 2*S*,4*R* isomer **6′** were confirmed by NOESY spectroscopy. The structures and absolute configurations of compounds **8**{*2*} and **11**{*1*;*1*} were confirmed by X-ray diffraction (see Supporting Information).

Conclusion

A parallel solution-phase synthesis of (2*S*,4*S*)-4-acylamino-5-oxopyrrolidine-2-carboxamides **11** from (*S*)-pyroglutamic

acid (**1**) via di-*tert*-butyl (2*S*,4*S*)-4-amino-5-oxopyrrolidine-1,2-dicarboxylate (**6**) as the key-intermediate was developed. In summary, 22 carboxamides **11** were synthesized. Special attention was paid to the last amidation step employing four different activating reagents: BPC or PFTU (method A), EEDQ (method B), and TBTU (method C). This study revealed that the coupling reagent has an important impact on the outcome of the reaction. BPC and PFTU (method A) were not suited, since diketopiperazines **15** were sometimes obtained instead of the desired carboxamides **11**. On the other hand, amidations with EEDQ (method B) and TBTU (method C) led to the desired carboxamides **11** exclusively. In terms of selectivity, EEDQ and TBTU can, thus, be regarded as equivalent reagents; however, in terms of purity, EEDQ was advantageous over TBTU.

Experimental Section

Materials and General Methods. Melting points were determined on a Kofler micro hot stage. The NMR spectra were obtained on a Bruker Avance DPX 300 at 300 MHz for ^{1}H and 75.5 MHz for ^{13}C nucleus, using DMSO-d_6 and $CDCl_3$ with TMS as the internal standard as solvents. All NMR experiments were carried out at 23 °C. Within the ^{1}H NMR spectral data, abbreviation deg is used for assignment of degenerate signals (e.g., deg t and deg dt) with two almost identical coupling constants. Optical rotations were measured on a Perkin-Elmer 241MC Polarimeter. Mass spectra were recorded on an AutoSpecQ spectrometer; IR spectra, on a Perkin-Elmer Spectrum BX FTIR spectrophotometer. Microanalyses were performed on a Perkin-Elmer CHN Analyzer 2400 II. The de of the crude oily free amine **6** and its crystalline salts was determined by ^{1}H NMR.

(*S*)-Pyroglutamic acid (**1**), acid chlorides **7**{*1*−*4*,*8*} and carboxylic acids **7**{*5*−*7*}, amines **10**{*1*−*6*}, BPC, PFTU, EEDQ (Sigma-Aldrich), and TBTU (Iris Biochem) are commercially available.

Parallel Synthesis. Parallel syntheses of compounds **11** were carried out on a Mettler-Toledo Bohdan MiniBlock Compact Shaking and Washing Station and Vacuum Collection Base (12 positions, vortex stirring, 400 rpm in all cases) for methods A and B and on a Tehtnica Železniki Vibromix 313 EVT orbital shaker (12-position vessel rack, vortex stirring, 400 rpm in all cases) for method C. All parallel evaporations were carried out on a Büchi Syncore Polyvap R-24 System (24 positions, vortex stirring, 400 rpm in all cases).

General Procedures for the Preparation of (2*S*,4*S*)-Di-*tert*-butyl 4-Acylamino-5-oxopyrrolidine-1,2-dicarboxylates 8{*1*−*8*}. General Procedure A. Amine **6** hydrochloride (1.684 g, 5 mmol) was suspended in anhydrous dichloromethane (20 mL), cooled to 0 °C (ice bath), and 4-methylmorpholine (1.65 mL, 15 mmol) was added. A solution of acid chloride **7** (7 mmol) in anhydrous CH_2Cl_2 (10 mL) was added dropwise at 0 °C to the stirred solution, and the mixture was stirred at room temperature (r.t.) for 2 h, then water (25 mL) and dichloromethane (25 mL) were added, the mixture was stirred for 5 min, and the phases were separated. The organic phase was washed subsequently with aq $NaHSO_4$ (1 M, 50 mL), brine (50 mL), and sat. aq $NaHCO_3$ (50 mL). The organic phase was dried over anhydrous sodium sulfate and filtered, and the filtrate was evaporated in vacuo. The residue was purified, either by FC on silica gel (EtOAc−hexanes, 1:1) or by crystallization (EtOAc−hexanes, ∼1:2), to give **8**. Compounds **8**{*1*−*4*,*8*} were prepared in this manner.

General Procedure B. Amine **6** hydrochloride (1.684 g, 5 mmol) was suspended in anhydrous dichloromethane (20 mL), carboxylic acid **7** (10.5 mmol) was added, and the mixture was stirred at 0 °C for 5 min. Then a solution of DCC (2.06 g, 10 mmol) in anhydrous CH_2Cl_2 (20 mL) was added and the mixture was stirred at 0 °C for 2 h. The precipitated DCU was filtered off and washed with dichloromethane (3 ×10 mL). The combined filtrate was washed subsequently with aq $NaHSO_4$ (1 M, 50 mL), brine (50 mL), and sat. aq $NaHCO_3$ (50 mL); dried over anhydrous sodium sulfate; and filtered, and the filtrate was evaporated in vacuo to give the oily **8**, which was used in the next step without purification. Compounds **8**{*5*−*7*} were prepared in this manner.

Experimental data for compounds **8**{*1*−*8*} are given in Table 1. Analytical and spectral data for compounds **8**{*1*−*8*} are given in the Supporting Information (Tables A and B).

General Procedure for the Preparation of (2*S*,4*S*)-4-Acylamino-5-oxopyrrolidine-2-carboxylic Acids 9{*1*−*8*}. A mixture of **8** (3 mmol), CH_2Cl_2 (18 mL), and trifluoroacetic acid (9 mL) was stirred at r.t. for 12 h. Volatile components were evaporated in vacuo, and the residue was triturated with Et_2O (45 mL). The precipitate was collected by filtration and washed with Et_2O (2 × 5 mL) to give **9**{*1*−*8*}. In this manner, analytically pure compounds **9**{*1*−*4*,*8*} were obtained from analytically pure precursors **8**{*1*−*4*,*8*}. Compounds **9**{*5*−*7*}, prepared from the crude precursors **8**{*5*−*7*}, were additionally recrystallized from water in order to reach analytical purity.

Experimental data for compounds **9**{*1*−*8*} are given in Table 1. Analytical and spectral data for compounds **9**{*1*−*8*} are given in the Supporting Information (Tables A and B).

General Procedures for Parallel Amidation of (2*S*,4*S*)-4-Acylamino-5-oxopyrrolidine-2-carboxylic Acids 9 with BPC or PFTU as the Activating Reagents (Method A). Procedure A. A MiniBlock with 12 positions (3 × 4) was assembled with fritted glass vessels; the acids **9** (1 mmol), anhydrous acetonitrile (10 mL), and triethylamine (0.14 mL, 1 mmol) were added; and the mixture was vortexed at 20 °C for 5 min. BPC (0.394 g, 1 mmol) or PFTU (0.285 g, 1 mmol) was added to each vessel, and the mixtures were vortexed for 1 h, then a solution of amines **10** and triethylamine in anhydrous acetonitrile (**10**/Et_3N = 1:1, 0.2 M, 5 mL, 1 mmol) were added to each vessel, and the mixtures were vortexed at 20 °C for 12 h. Finally, water (1 mL, 56 mmol) and triethylamine (0.84 mL, 6 mmol) were added to each vessel, and vortexing at 20 °C was continued for 24 h. The reaction mixtures were filtered, and the filtrates were evaporated in vacuo (0.1 Torr/60 °C) to give **11** and **15**. Compounds **11**{*2*;*1*,*2*}, **11**{*3*;*1*−*4*}, and **15**{*3*} were prepared in this manner.

Procedure B. A MiniBlock with 12 positions (3 × 4) was assembled with fritted glass vessels; the acids **9** (1 mmol), anhydrous acetonitrile (10 mL), and triethylamine (0.14 mL, 1 mmol) were added; and the mixture was vortexed at 20 °C for 5 min. BPC (0.394 g, 1 mmol) or PFTU (0.285 g, 1 mmol) was added to each vessel, and the mixtures were vortexed for 1 h. Then solutions of amines **10** and triethylamine in anhydrous acetonitrile (**10**/Et_3N = 1:1, 0.2 M, 5 mL, 1 mmol) were added to each vessel, and the mixtures were vortexed at 20 °C for 12 h. The precipitates were collected by filtration and washed with acetonitrile (2 mL) to give **11** and **15**. Compounds **11**{*1*;*4*,*6*}, **11**{*2*;*3*,*4*}, **11**{*4*;*5*}, **11**{*5*;*3*−*5*}, **11**{*6*;*3*,*4*}, and **15**{*2*,*4*,*5*} were prepared in this manner.

Experimental data for compounds **11**{*1*;*4*,*6*}, **11**{*2*;*1*−*4*}, **11**{*3*;*3*,*4*}, **11**{*4*;*5*}, **11**{*5*;*3*−*5*}, **11**{*6*;*3*,*4*}, and **15**{*2*−*5*} are given in Table 2. Analytical and spectral data for **11** and **15** are given in the Supporting Information (Tables C and D).

General Procedures for Parallel Amidation of (2*S*,4*S*)-4-Acylamino-5-oxopyrrolidine-2-carboxylic Acids 9 with EEDQ as the Activating Reagent. Procedure A. A MiniBlock with 12 positions (3 × 4) was assembled with fritted glass vessels; the acids **9**{*1*−*5*,*7*} (0.4 mmol), anhydrous DMSO (0.5 mL), and anhydrous dichloromethane (4.5 mL) were added; and the suspensions were vortexed at r.t. for 5 min. Solutions of primary amines **10**{*3*−*6*} (0.2 M in CH_2Cl_2, 2.1 mL, 0.42 mmol) were added, and the so-formed suspensions were vortexed at r.t. for 10 min. Then a solution of EEDQ (0.2 M in CH_2Cl_2, 2.1 mL, 0.42 mmol) was added to each vessel, and the mixtures were vortexed at r.t. for 24 h. The precipitates were collected by filtration and washed with dichloromethane to give **11**. Compounds **11**{*1*−*3*;*3*,*4*}, **11**{*4*;*3*}; **11**{*5*;*5*,*6*}, and **11**{*7*;*3*} were prepared in this manner.

Procedure B. A MiniBlock with 12 positions (3 × 4) was assembled with fritted glass vessels, the acids **9**{*1*−*3*,*5*} (0.4 mmol) and anhydrous dichloromethane (5 mL) were added, and the suspensions were vortexed at r.t. for 5 min. Solutions of secondary amines **10**{*1*,*2*} (0.2 M in CH_2Cl_2, 2.1 mL, 0.42 mmol) were added, and the so-formed suspensions were vortexed at r.t. for 10 min. Then a solution of EEDQ (0.2 M in CH_2Cl_2, 2.1 mL, 0.42 mmol) was added to each vessel, and the mixtures were vortexed at r.t. for 24 h. The reaction mixtures were filtered, and the filtrates were chromatographed through a column filled with basic alumina (1 × 5 cm). First, most of the quinoline and nonpolar impurities were eluted with CH_2Cl_2 (75 mL of eluate, fraction 1). The rest of the quinoline and some other impurities were eluted with EtOAc (75 mL of eluate, fraction 2). The products **11** were eluted with EtOAc−EtOH (5:1, 120 mL of eluate, fraction 3). Fractions 3 were evaporated in vacuo to give the purified carboxamides **11**. Compounds **11**{*1*−*3*;*1*,*2*} and **11**{*5*;*1*} were prepared in this manner.

Experimental data for compounds **11**{*1*−*3*;*1*−*4*}, **11**{*4*;*3*}, **11**{*5*;*1*,*5*,*6*}, and **11**{*7*;*3*} are given in Table 2. Analytical and spectral data for compounds **11** are given in the Supporting Information (Tables C and D).

General Procedure for Parallel Amidation of (2*S*,4*S*)-4-Acylamino-5-oxopyrrolidine-2-carboxylic Acids 9 with TBTU as the Activating Reagent (Method C). An orbital shaker was equipped with a rack containing 12 glass vials. The acids **9** (0.2 mmol), anhydrous acetonitrile (1 mL), and a solution of triethylamine in anhydrous acetonitrile (0.2 M, 1 mL, 0.2 mmol) were added to the vessels, and the mixtures were vortexed at r.t. for 30 min. TBTU (0.064 g, 0.2 mmol) was added to each vessel, and vortexing at r.t. was continued for 1 h. Then solutions of amines **10**{*1*−*4*} in anhydrous acetonitrile (0.1 M, 2 mL, 0.2 mmol) were added, and the mixtures were vortexed at r.t. for 24 h. Volatile components were evaporated in vacuo to give the crude carboxamides **11**, which were dissolved in DMF (3 mL) and poured on a short column filled with basic alumina (3.5 g, 1 × 3 cm, stabilized with DMF), and the products were eluted with DMF−MeOH (9:1, 60 mL). The eluates were evaporated in vacuo (1 mbar, 50 °C) to give **11**. Compounds **11**{*1*−*3*;*1*−*4*} were prepared in this manner.

Experimental data for compounds **11**{*1*−*3*;*1*−*4*} are given in Table 3. Analytical and spectral data for compounds **11** are given in the Supporting Information (Tables C and D).

Acknowledgment. The financial support from Boehringer-Ingelheim Pharma (Biberach, Germany) is gratefully acknowledged. We are grateful for the financial support from the Slovenian Research Agency through grants P1-0179 and J1-6689-0103-04. We acknowledge with thanks the financial contributions of pharmaceutical companies Krka d.d. (Novo mesto, Slovenia) and Lek d.d., a new Sandoz Company (Ljubljana, Slovenia), which made the purchase of the Mettler-Toledo Bohdan MiniBlock Compact Shaking and Washing Station and Vacuum Collection Base possible.

Supporting Information Available. Experimental, analytical, and spectral data for compounds **2**−**6**; analytical and spectral data for compounds **8**, **9**, **11**, and **15**; structure determination (NOESY spectroscopy, X-ray diffraction) for compounds **6**, **8**{*2*}, and **11**{*1*;*1*}. This material is available free of charge via the Internet at http://pubs.acs.org.

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CC060114S