Tetrahedron 66 (2010) 6174–6180

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

γ-Lactam-containing peptidomimetics

Mickael Virlouvet, Joachim Podlech *

Institut für Organische Chemie, Karlsruher Institut für Technologie (KIT), Fritz-Haber-Weg 6, 76131 Karlsruhe, Germany

ARTICLE INFO

Article history:
Received 17 February 2010
Received in revised form 10 May 2010
Accepted 26 May 2010
Available online 4 June 2010

Keywords:
Amino acids
Pyrrolidinones
Pyrrolidines
Peptidomimetics
Peptide coupling

ABSTRACT

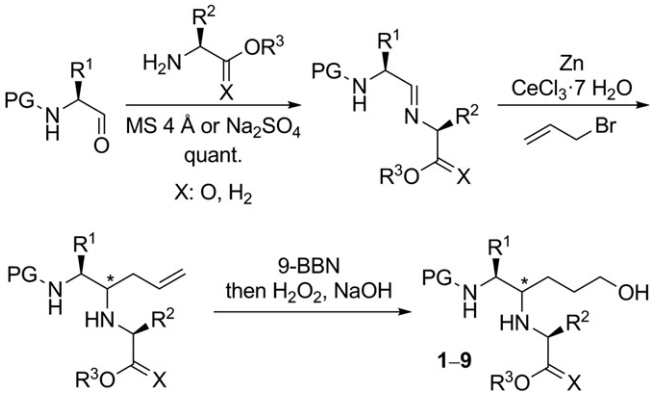
Protected diaminoalcohols obtained through allyl addition to α-amino acid-derived imines and subsequent hydroboration were used for the preparation of pyrrolidinones and pyrrolidines. Pyrrolidinones were synthesized with moderate yields by oxidation of the hydroxy function with tetrapropylammonium perruthenate/*N*-methylmorpholine-*N*-oxide and concomitant cyclization while pyrrolidines were synthesized in good yields by tosylation of the hydroxy group and subsequent intramolecular nucleophilic substitution. Thus accessible substrates were transferred into peptidomimetics by attachment of amino acid moieties at both termini using conventional peptide coupling strategies. Molecular mechanics optimizations suggest that these substrates preferentially adopt a turn conformation.

1. Introduction

Peptides showing a turn conformation[1] are of major relevance since, in most cases, these turn regions are responsible for the biological activity of the respective peptide. Well known representatives showing a turn conformation are, inter alia, somatostatin[2] and oxytocin.[3] Substrates containing rigid frameworks, i.e., turn mimics, can be prepared by replacement of the turn region with other, mostly cyclic templates.[4] Among other heterocyclic scaffolds, lactams have successfully been used as turn-inducing moieties.[5] In our ongoing research on the preparation of peptidomimetics,[6] we recently prepared amino acid-derived β-lactams suitable as scaffolds for β-turn mimetics.[7] In this paper we present the utilization of γ-lactams and similar compounds as building blocks for the synthesis of peptidomimetics.

2. Synthesis of pyrrolidines and pyrrolidinones

α-Amino acid-derived pyrrolidinones and pyrrolidines suitable for the synthesis of peptidomimetics were prepared starting with diaminoalcohols **1**–**9** whose preparation has been published by us previously.[8] Their synthesis comprises allyl addition to α-amino acid-derived imines and hydroboration using 9-borabicyclo[3.3.1]nonane (9-BBN) followed by oxidative work-up (Scheme 1).



Scheme 1. Synthesis of α-amino acid-derived diaminoalcohols.

Oxidation of the alcohol function was necessary for the pyrrolidinone synthesis. The tested methods are summarized in Table 1. Neither Dess–Martin's periodinane (DMP, entry 1), which was reported to be a suitable oxidation agent for the oxidation of alcohols to aldehydes and furthermore for the oxidation of lactols to lactones,[9] nor 2-iodoxybenzoic acid (IBX, entry 2)[10] or 2,2,6,6-tetramethylpiperidinyloxyl (TEMPO)/NaOCl (entry 3)[11] did yield the respective aldehydes or pyrrolidinones when alcohol **1** was used as substrate. Direct oxidation to the pyrrolidinone was furthermore

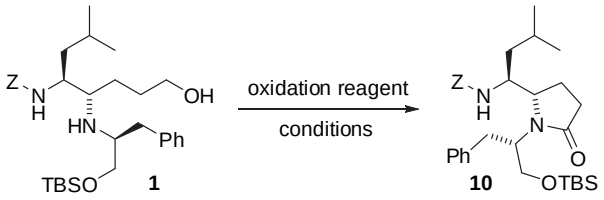
Abbreviations: DMAP, 4-dimethylaminopyridine; HATU, 2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate; NMO, N-methylmorpholin-N-oxid; TBS, tert-butyldimethylsilyl; TBDPS, tert-butyldiphenylsilyl; Tos, 4-toluenesulfonyl; TPAP, tetrapropylammonium perruthenate.

* Corresponding author. Tel.: +49 721 608 3209; fax: +49 721 608 7652; e-mail address: joachim.podlech@kit.edu (J. Podlech).

0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.05.099

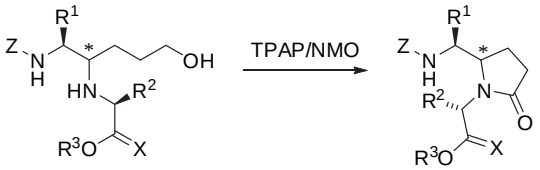
not achieved with pyridinium dichromate (PDC),[12] with TEMPO/$PhI(OAc)_2$[13] or with Jones' reagent[14] (CrO_3, H_2SO_4, acetone; entries 4–6). While utilization of $RuCl_3/NaIO_4$[15] (entry 7) led to the formation of pyrrolidinone **10** with 39% yield, a similar yield (35%) was achieved with catalytic amounts of tetrapropylammonium perruthenate (TPAP) and *N*-methylmorpholine-*N*-oxide (NMO) as co-oxidant (entry 8).[16] The latter conditions in due course turned out to give best results and were successfully applied to the preparation of the pyrrolidinones **10**–**16** (Table 2).

Table 1
Conditions used in pyrrolidinone synthesis



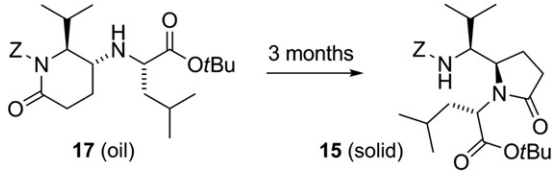
#	Reagent (equiv)	Conditions	Yield [%]
1	DMP (2.5)	CH_2Cl_2, rt	—
2	IBX (1.1)	AcOEt, reflux	—
3	TEMPO/NaOCl (0.2/1.1)	toluene/AcOEt/H_2O (6:6:1), 0 °C	—
4	PDC (2)	CH_2Cl_2, 0 °C to rt	—
5	TEMPO/$PhI(OAc)_2$ (0.1/2.2)	CH_2Cl_2, rt	—
6	Jones' reagent (4)	acetone, 0 °C	—
7	$RuCl_3/NaIO_4$ (0.03/4.1)	$CCl_4/CH_3CN/H_2O$ (1:1:1.5), 0 °C	39
8	TPAP/NMO (0.1/3)	CH_2Cl_2, 0 °C to rt	35

Table 2
Synthesis of pyrrolidinones



Alcohol	Config.	R^1	R^2	X	R^3	Product	Yield [%]
1	*S*	^{i}Bu	Bn	H,H	TBS	**10**	35
2	*S*	^{i}Pr	Me	H,H	TBS	**11**	32
3	*S*	^{i}Pr	Me	H,H	TBDPS	**12**	43
4	*S*	Me	^{i}Bu	O	^{t}Bu	**13**	38
5	*R*	^{i}Pr	Bn	O	^{t}Bu	**14**	25
6	*R*	^{i}Pr	^{i}Bu	O	^{t}Bu	**15**	44
7	*S*	^{i}Pr	Bn	O	^{t}Bu	**16**	52

The moderate yields are most probably due to side reactions evolving from possible iminium intermediates[17] and due to formation of a side product (e.g., **17**), which was obtained in changing yields. This δ-lactam **17**, which was initially obtained, did not turn out to be stable with respect to a conversion into the desired solid **15** within some months (Scheme 2). Figure 1 depicts the complete conversion of δ-lactam **17** over a period of approximately three months.



Scheme 2. Conversion of δ-lactam **17** into γ-lactam **15**.

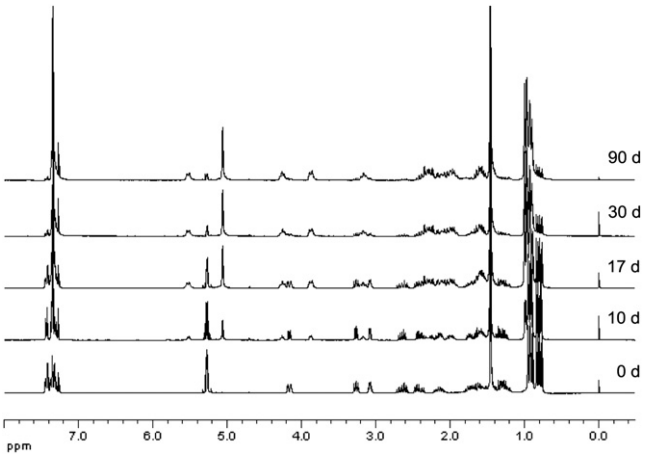
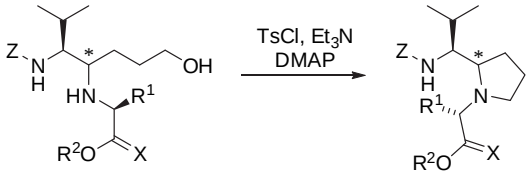


Figure 1. Conversion of δ-lactam **17** as monitored by ^{1}H NMR spectroscopy.

Preparation of pyrrolidines **18**–**21** was possible by slight variation of a method published by Alexakis et. al.[18] The hydroxy function in compounds **3** and **7**–**9** was converted with *p*-toluenesulfonyl chloride, triethylamine, and a catalytic amount of *p*-dimethylaminopyridine (DMAP) into a good leaving group. The subsequent spontaneous ring closure led to pyrrolidines **18**–**21** with good yields (Table 3).

Table 3
Synthesis of pyrrolidines

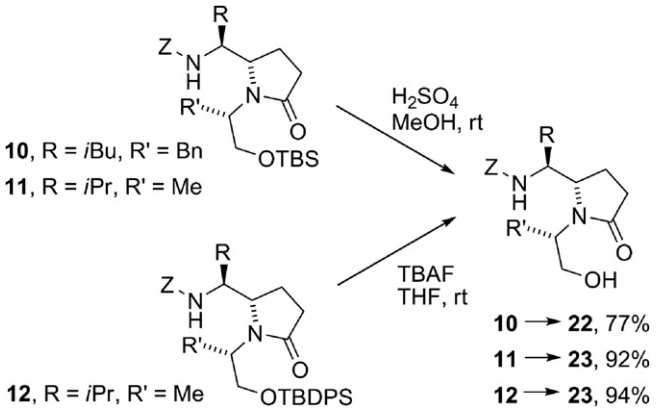


#	Alcohol	Config.	R^1	X	R^2	Product	Yield [%]
1	**3**	*S*	Me	H,H	TBDPS	**18**	88
2	**8**	*S*	^{i}Bu	O	^{t}Bu	**19**	78
3	**7**	*S*	Bn	O	^{t}Bu	**20**	80
4	**9**	*R*	^{i}Pr	O	^{t}Bu	**21**	71

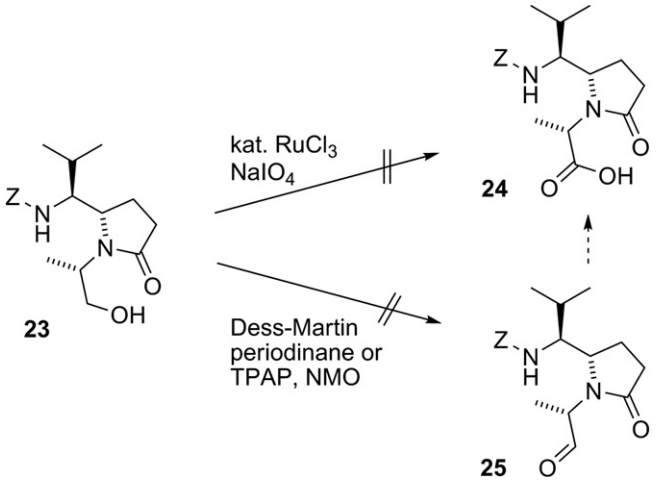
3. Synthesis of peptidomimetics

Thus the obtained pyrrolidinones and pyrrolidines were available for the preparation of peptidomimetics. For this purpose, further α-amino acids were supposed to be attached at the termini with conventional peptide coupling strategies. Silyloxy-derivatives **10**–**12** and **18** had to be transferred into the corresponding carboxylic acids. Desilylation was cleanly achieved with good yields with either catalytic amounts of sulfuric acid in methanol (TBS derivatives, Scheme 3)[19] or with tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (TBDPS derivative).[19,20]

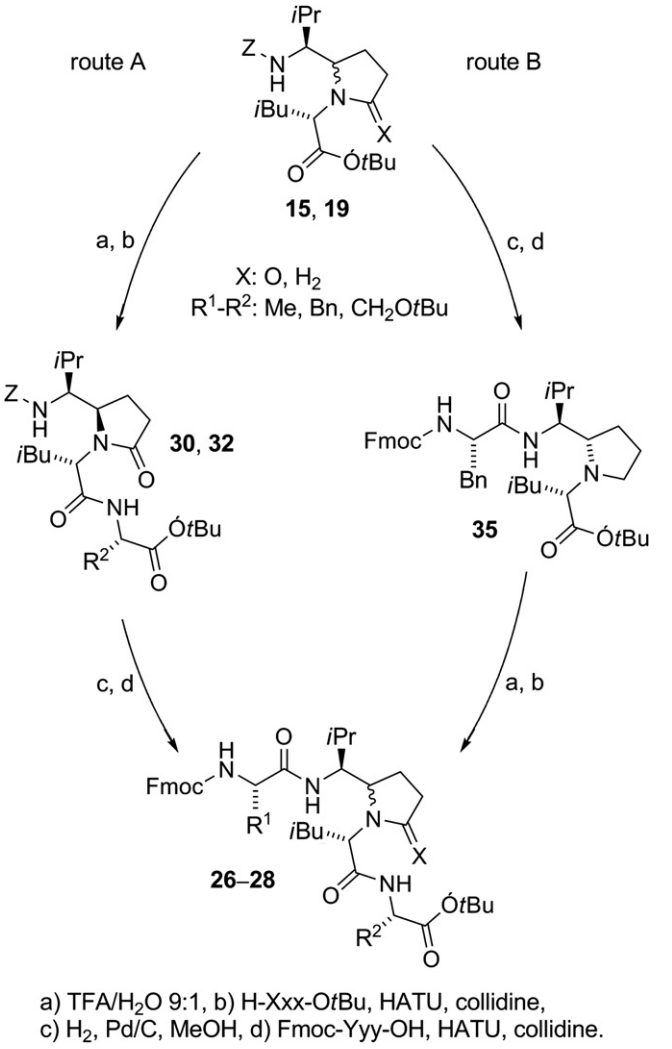
Oxidation of the obtained alcohol **23** to carboxylic acid **24** was not achieved with catalytic amounts of ruthenium trichloride and sodium periodate as co-oxidant (Scheme 4).[21] While a consumption of the alcohol was observed, no defined product could be identified in the reaction mixture. A two-step protocol with oxidation to an aldehyde with subsequent oxidation into the carboxylic acid similarly failed, since formation of the aldehyde was neither achieved with tetrapropylammonium perruthenate/*N*-methylmorpholine-*N*-oxide (TPAP/NMO) nor with Dess–Martin's periodinane. Consequently a use of these intermediates was not further considered in the preparation of peptidomimetics.



Scheme 3. Deprotection of silyl protection groups.



Scheme 4. Attempts to achieve oxidation of alcohol **23**.



Scheme 5. Synthesis of peptidomimetics.

To obtain *pseudo*-tetrapeptides from pyrrolidinones **13**–**16** and pyrrolidines **19**–**21** two strategies are possible. Route A comprises the cleavage of the *tert*-butyl ester with coupling of a further amino acid,[22] deprotection of the N-terminal protection group and again attachment of a further amino acid. Route B consists of the same steps in reversed order (Scheme 5).

Both routes were tested in the synthesis of *pseudo*-tetrapeptides **26**–**28** (Fig. 2). Route A was used for the preparation of **26** and route B was used for the synthesis of **28**. Compound **27** was prepared via both routes. Route A turned out to afford the desired compounds in significantly better yields than route B, possibly due the formation of a side product **29** formed during N-terminal deprotection in route B. This side product is an analog of a diketopiperazide; its formation should be favored by the proline-like scaffold, which is known to enforce a cyclization.[23] When pyrrolidinone **14** was reacted according to route B, this side product was obtained quantitatively (Scheme 6), despite the fact that a *tert*-butyl ester should prevent a lactam formation. This gives clear evidence that these compounds tend to form a turn structure, thus favoring this cyclization (vide infra).

pseudo-Tetrapeptides **26**–**28** were obtained as foamy solids, which could not be transferred into crystals suitable for X-ray crystallographic analysis. Interpretation of NOESY and ROESY spectra was not possible due to a severe overlap of signals. Consequently a comprehensive investigation on the preferred conformations in these compounds was not possible. Nevertheless, molecular mechanics optimizations (MM2)[24] gave evidence that both the pyrrolidinone- and the pyrrolidine-derived peptidomimetics **27** and **28** adopt a turn-conformation stabilized by hydrogen bonds between the incoming and the leaving strand (Fig. 3). The obtained structures do not allow a classification into

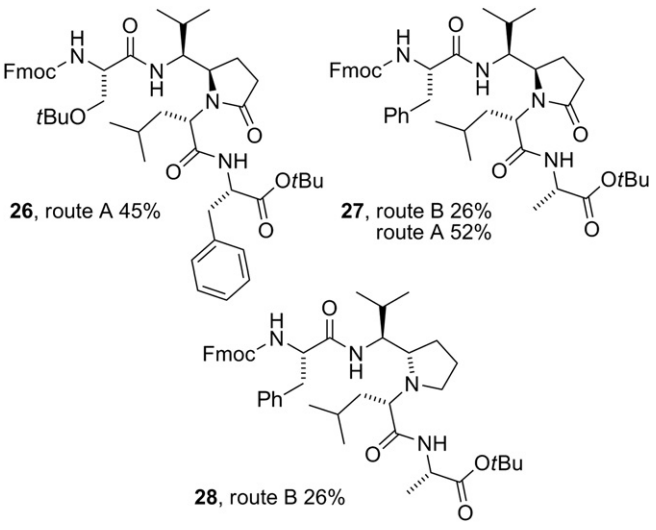
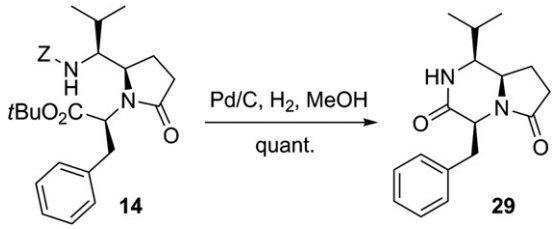


Figure 2. Synthesized *pseudo*-tetrapeptides.



Scheme 6. Side reaction during hydrogenolysis.

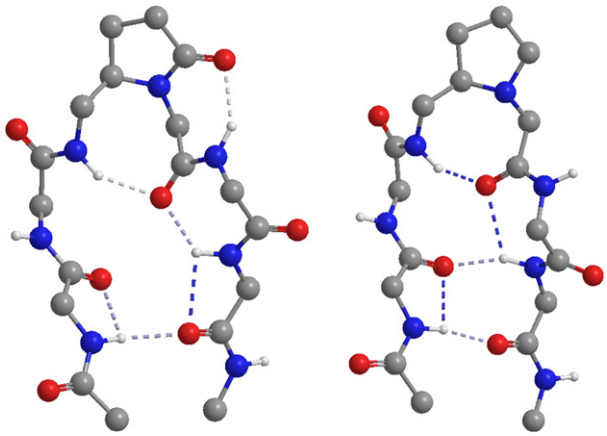


Figure 3. Peptides containing the core of **27** (left) and **28** (right) optimized using a MM2 force field (non-polar hydrogen atoms and side chains are omitted here for clarity but were considered during optimizations).[24]

given turn types.[1] Compounds **27** and **28** uncommonly show hydrogen bonds in the turn region between the N–H of the incoming strand with the C=O group of the leaving strand. Most published turn mimics shown hydrogen bonds vice versa from N–H of the leaving strand to a C=O of the incoming strand. Compound **27** is additionally stabilized by a further hydrogen bond with participation of the pyrrolidinone carbonyl group leading to a somewhat more open angle between incoming and leaving peptide strands.

4. Experimental section

4.1. General remarks

Compounds **1**–**9** were prepared as described previously.[8] Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl radical and CH_2Cl_2 was distilled from CaH_2. All moisture-sensitive reactions were carried out under oxygen-free argon or N_2 using oven-dried glassware and a vacuum line. Flash column chromatography[25] was carried out using Merck silica gel 60 (230–400 mesh) and thin layer chromatography (TLC) was carried out using commercially available Merck F_{254} pre-coated sheets. HPLC analyses were carried out with a Merck-Hitachi LaChrom D7000 apparatus with a L7100 mixer and diode-array detection (L7455) on a LiChrospher Si 60, 5 μm, Merck (flow: 1–1.5 ml/min) chromatographic column. ^1H and ^{13}C NMR spectra were recorded on a Bruker Cryospek WM-250, an AM-400 or a DRX 500. Chemical shifts are given in parts per million downfield of tetramethylsilane. ^{13}C NMR spectra were recorded with broad band proton decoupling and were assigned using DEPT 135 and DEPT 90 experiments. Melting points were measured on a Büchi apparatus. IR spectra were recorded on a Bruker IFS-88 spectrometer. Elemental analyses were performed on a Heraeus, CHN–O-rapid or on an elementar vario MICRO. Electrical ionization and high resolution mass spectra were recorded on a Finnigan MAT-90. Optical rotations were recorded on a Perkin Elmer 241 polarimeter (using the sodium D line, 589 nm) and specific optical rotations [α] are given in units of $10^{-1}\cdot deg\cdot cm^2\cdot g^{-1}$. Detailed spectroscopic data are given as supplementary data.

4.2. Synthesis of pyrrolidinones

*4.2.1. (2S,1′S,2″S)-5-(1-Benzyloxycarbonylamino-3-methyl-butyl)-1-(1-tert-butyldimethylsilyloxy-3-phenyl-propan-2-yl)pyrrolidin-2-one (**10**).* TPAP (73 mg, 0.02 mmol) was added to a suspension of alcohol **1** (1.15 g, 2.07 mmol), NMO (837 mg, 6.20 mmol), and MS 4 Å (1.00 g) in CH_2Cl_2 (5 mL). The mixture was stirred for 3 h at rt (monitoring with TLC), filtered (Celite), concentrated, and purified by chromatography (silica gel, 200 mm×25 mm Ø, hexanes/EtOAc 3:1) to yield pyrrolidinone **10** (397 mg, 0.72 mmol, 35%) as a colorless solid.

*4.2.2. (5S,1′S,2″S)-5-(1-Benzyloxycarbonylamino-3-methyl-propyl)-1-(1-tert-butyldimethylsilyloxy-propan-2-yl)pyrrolidin-2-one (**11**).* TPAP (118 mg, 0.33 mmol) was added to a suspension of alcohol **2** (1.56 g, 3.34 mmol), NMO (1.35 g, 10.0 mmol), and MS 4 Å (1.67 g) in CH_2Cl_2 (5 mL). The mixture was stirred for 3 h at rt (monitoring with TLC), filtered (Celite), concentrated, and purified by chromatography (silica gel, 200 mm×25 mm Ø, hexanes/EtOAc 2:1→1:1) to yield pyrrolidinone **11** (500 mg, 1.08 mmol, 32%) as a yellow oil.

*4.2.3. (5S,1′S,1″S)-5-(1-Benzyloxycarbonylamino-2-methyl-propyl)-1-(1-tert-butyldiphenylsilyloxy-propan-2-yl)pyrrolidin-2-one (**12**).* TPAP (52 mg, 0.15 mmol) was added to a suspension of alcohol **3** (868 mg, 1.47 mmol), NMO (596 mg, 4.40 mmol), and MS 4 Å (750 mg) in CH_2Cl_2 (5 mL). The mixture was stirred for 3 h at rt (monitoring with TLC), filtered (Celite), concentrated, and purified by chromatography (silica gel, 200 mm×30 mm Ø, hexanes/EtOAc 4:1→2:1) to yield pyrrolidinone **12** (501 mg, 0.85 mmol, 43%) as a yellow oil.

*4.2.4. tert-Butyl (2S,2′S,1″S)-2-[2-(1-benzyloxycarbonylamino-ethyl)-5-oxo-pyrrolidin-1-yl]-4-methyl-pentanoate (**13**).* TPAP (5 mg, 14 μmol) was added to a suspension of alcohol **4** (120 mg, 0.27 mmol), NMO (89 mg, 0.66 mmol), and MS 4 Å (137 mg) in CH_2Cl_2 (5 mL). The mixture was stirred for 3 h at rt (monitoring with TLC), filtered (Celite), concentrated, and purified by chromatography (silica gel, 150 mm×15 mm Ø, hexanes/EtOAc 2:1→1:1) to yield pyrrolidinone **13** (45 mg, 0.10 mmol, 38%) as a yellow oil.

*4.2.5. tert-Butyl (2S,2′R,1″S)-2-[2-(1-benzyloxycarbonylamino-2-methyl-propyl)-5-oxo-pyrrolidin-1-yl]-3-phenyl-propanoate (**14**).* TPAP (37 mg, 0.11 mmol) was added to a suspension of alcohol **5** (519 mg, 1.05 mmol), NMO (300 mg, 2.52 mmol), and MS 4 Å (500 mg) in CH_2Cl_2 (5 mL). The mixture was stirred for 3 h at rt (monitoring with TLC), filtered (Celite), concentrated, and purified by chromatography (silica gel, 200 mm×25 mm Ø, hexanes/EtOAc 2:1→1:1) to yield pyrrolidinone **14** (129 mg, 0.26 mmol, 25%) as a yellow solid.

*4.2.6. tert-Butyl (2S,2′R,1″S)-2-[2-(1-benzyloxycarbonylamino-2-methyl-propyl)-5-oxo-pyrrolidin-1-yl]-4-methyl-pentanoate (**15**).* TPAP (408 mg, 1.16 mmol) was added to a suspension of alcohol **6** (5.39 g, 11.6 mmol), NMO (3.76 g, 27.8 mmol), and molecular sieves (4 Å, 5.80 g) in CH_2Cl_2 (30 mL). The mixture was heated to reflux for 2 h (monitoring with TLC), cooled, filtered (Celite), concentrated, and purified by chromatography (silica gel, 200 mm×45 mm Ø, hexanes/EtOAc 2:1→1:1) to yield pyrrolidinone **15** (2.36 g, 5.13 mmol, 44%) as

a yellow solid and side product **17** (600 mg, 1.30 mmol, 11%) as a yellow oil.

*4.2.7. tert-Butyl (2S,2′S,1″S)-2-[2-(1-benzyloxycarbonylamino-2-methyl-propyl)-5-oxo-pyrrolidin-1-yl]-3-phenyl-propanoate (**16**).* TPAP (141 mg, 0.40 mmol) was added to a suspension of alcohol **7** (2.00 g, 4.00 mmol), NMO (1.30 g, 9.60 mmol), and molecular sieves (4 Å, 2.00 g) in CH_2Cl_2 (10 mL). The mixture was heated to reflux for 2 h (monitoring with TLC), cooled, filtered (Celite), concentrated, and purified by chromatography (silica gel, 200 mm×45 mm Ø, hexanes/EtOAc 4:1→2:1) to yield pyrrolidinone **16** (1.03 g, 2.08 mmol, 52%) as a yellow oil.

4.3. Synthesis of pyrrolidines

*4.3.1. (2S,1′S,2″S)-2-[1-(Benzyloxycarbonylamino)-2-methyl-propyl]-1-(tert-butyldiphenylsilyloxy-prop-2-yl)pyrrolidine (**18**).* TosCl (200 mg, 1.05 mmol) was added at rt to a solution of alcohol **3** (591 mg, 1.00 mmol), Et_3N (152 μL, 1.10 mmol), and a catalytic amount of DMAP in CH_2Cl_2 (10 mL). The reaction was stopped after stirring for 18 h by addition of saturated aqueous $NaHCO_3$ solution (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3×5 mL) and the combined organic layers were dried (Na_2SO_4), concentrated, and purified by chromatography (silica gel, 200 mm×30 mm Ø, hexanes/EtOAc 3:1) to yield pyrrolidine **18** (506 mg, 0.88 mmol, 88%) as a yellowish oil.

*4.3.2. tert-Butyl (2S,2′S,1″S)-2-[2-(1-benzyloxycarbonylamino-2-methyl-propyl)-pyrrolidin-1-yl]-4-methyl-pentanoate (**19**).* TosCl (2.22 g, 11.7 mmol) was added at room temperature to a solution of alcohol **8** (5.16 g, 11.1 mmol), Et_3N (1.85 mL, 13.3 mmol), and DMAP (136 mg, 1.1 mmol) in CH_2Cl_2 (70 mL). After stirring for 15 h saturated aqueous $NaHCO_3$ solution (50 mL) was added, the aqueous layer was extracted with CH_2Cl_2 (3×50 mL) and the combined organic layers were dried (Na_2SO_4), concentrated, and purified by chromatography (silica gel, 200 mm×45 mm Ø, hexanes/EtOAc 7:1) to yield pyrrolidine **19** (3.89 g, 8.70 mmol, 78%) as a yellowish oil.

*4.3.3. tert-Butyl (2S,2′S,1″S)-2-[2-(1-benzyloxycarbonylamino-2-methyl-propyl)pyrrolidin-1-yl]-3-phenylpropanoate (**20**).* TosCl (400 mg, 2.10 mmol) was added at rt to a solution of alcohol **7** (997 mg, 2.00 mmol), Et_3N (334 μL, 2.40 mmol), and a catalytic amount of DMAP in CH_2Cl_2 (15 mL). The reaction was stopped after stirring for 18 h by addition of saturated aqueous $NaHCO_3$ solution (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3×5 mL) and the combined organic layers were dried (Na_2SO_4), concentrated, and purified by chromatography (silica gel, 200 mm×30 mm Ø, hexanes/EtOAc 6:1→4:1) to yield pyrrolidine **20** (766 mg, 1.59 mmol, 80%) as a yellowish oil.

*4.3.4. tert-Butyl (2S,2′R,1″S)-2-[2-(1-benzyloxycarbonylamino-2-methyl-propyl)pyrrolidin-1-yl]-3-methyl-butanoate (**21**).* TosCl (264 mg, 1.38 mmol) was added at rt to a solution of alcohol **9** (594 mg, 1.32 mmol), Et_3N (220 μL, 1.58 mmol), and a catalytic amount of DMAP in CH_2Cl_2 (10 mL). The reaction was stopped after stirring for 18 h by addition of saturated aqueous $NaHCO_3$ solution (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3×5 mL) and the combined organic layers were dried (Na_2SO_4), concentrated, and purified by chromatography (silica gel, 200 mm×25 mm Ø, hexanes/EtOAc 6:1) to yield pyrrolidine **21** (406 mg, 0.94 mmol, 71%) as a yellowish oil.

4.4. Synthesis of pyrrolidinone-derived peptidomimetics

*4.4.1. (5S,1′S,2″S)-5-(1-Benzyloxycarbonylamino-3-methyl-butyl)-1-(1-hydroxy-3-phenyl-propan-2-yl)pyrrolidin-2-one (**22**).* Concentrated H_2SO_4 (two drops) was added at room temperature to a solution of *O*-TBS-protected alcohol **10** (316 mg, 0.57 mmol) in MeOH (5 mL). After stirring for 15 h the mixture was concentrated, digerated with Et_2O (10 mL), washed with H_2O (3×3 mL), dried (Na_2SO_4), concentrated, and purified by chromatography (silica gel, 200 mm×25 mm Ø, CH_2Cl_2/MeOH 20:1) to yield alcohol **22** (296 mg, 0.85 mmol, 77%) as a colorless solid.

*4.4.2. (5S,1′S,2″S)-5-(1-Benzyloxycarbonylamino-2-methyl-propyl)-1-(1-hydroxy-propan-2-yl)pyrrolidin-2-one (**23**).* Method (1) Concentrated H_2SO_4 (two drops) was added at room temperature to a solution of *O*-TBS-protected alcohol **11** (429 mg, 0.93 mmol) in MeOH (5 mL). After stirring for 15 h the mixture was concentrated, digerated with Et_2O (10 mL), washed with H_2O (3×3 mL), dried (Na_2SO_4), concentrated, and purified by chromatography (silica gel, 200 mm×25 mm Ø, CH_2Cl_2/MeOH 20:1) to yield alcohol **23** (192 mg, 0.44 mmol, 92%) as a yellow oil.

Method (2) TBAF (1.04 g, 3.30 mmol) was added portionwise at 0 °C to a solution of *O*-TBDPS-protected alcohol **12** (242 mg, 0.41 mmol) in THF (3 mL) and the mixture was stirred for 15 h at room temperature, concentrated, and purified by chromatography (silica gel, 200 mm×25 mm Ø, CH_2Cl_2/acetone 10:1→5:1) to yield alcohol **23** (134 mg, 0.38 mmol, 94%) as a yellow oil.

*4.4.3. (1S,4S,8bS)-4-Benzyl-tetrahydro-1-isopropylpyrrolo[1,2-a]pyrazine-3,6(4H,7H)-dione (**29**).* A suspension of Z-protected substrate **14** (944 mg, 1.91 mmol) and Pd/C (5%, 407 mg, 0.19 mmol) in anhydrous MeOH (10 mL) was stirred for 5 h under a hydrogen atmosphere. The mixture was filtrated (Celite) after complete consumption (monitoring with TLC) and the filtrate was concentrated to yield heterocycle **29** (547 mg, quant.) as a yellow solid.

*4.4.4. tert-Butyl (2S,2′S,2″R,1‴S)-2-{2-[2-(1-benzyloxycarbonylamino-2-methyl-propyl)-5-oxo-pyrrolidin-1-yl]-4-methyl-pentanoylamino}-propanoate (**30**).* TFA/H_2O (9:1, 1.1 mL) was added to *tert*-butyl ester **15** (465 mg, 1.00 mmol), the mixture was concentrated and the resulting carboxylic acid was used without further purification. Collidine (662 μL, 5.00 mmol) was added at 0 °C to a solution of the carboxylic acid (404 mg, 1.00 mmol), HATU (951 mg, 2.50 mmol), and H–Ala–O^{t}Bu (363 mg, 2.50 mmol) in DMF (5 mL). The mixture was stirred for 16 h, poured into H_2O (500 mL), and extracted with Et_2O (4×25 mL). The combined organic layers were washed with H_2O (2×30 mL) and brine (30 mL), dried (Na_2SO_4), concentrated, and purified (silica gel, 200 mm×25 mm Ø, CH_2Cl_2/acetone 10:1) to yield product **30** (406 mg, 0.76 mmol, 76%) as a colorless foam.

*4.4.5. tert-Butyl (2S,2′S,2″R)-2-{2-[2-(1-amino-2-methyl-propyl)-5-oxo-pyrrolidin-1-yl]-4-methyl-pentanoylamino}-propanoate (**31**).* A suspension of carbamate **30** (319 mg, 0.60 mmol) and Pd/C (5%, 128 mg, 0.06 mmol) in anhydrous MeOH (5 mL) was stirred under a hydrogen atmosphere until completion of the hydrogenolysis (monitoring with TLC). The mixture was filtered (Celite), concentrated, and used for the peptide coupling without further purification as a colorless oil (240 mg, 0.60 mmol, quant.).

*4.4.6. tert-Butyl (2S,2′S,2″R,1‴S,2⁗S)-2-[2-(2-{1-[2-(9H-fluoren-9-ylmethoxycarbonylamino)-3-phenyl-propionylamino]-2-methyl-propyl}-5-oxo-pyrrolidin-1-yl)-4-methyl-pentanoylamino]-propanoate (**27**).* Collidine (224 μL, 205 mg, 1.69 mmol) was added at 0 °C to a solution of amine **31** (239 mg, 0.60 mmol), HATU (321 mg, 0.85 mmol), and Fmoc–Phe–OH (327 mg, 0.85 mmol) in DMF (5 mL). The mixture was stirred for 16 h, poured into H_2O (500 mL), and extracted with Et_2O (4×25 mL). The combined organic layers were washed with H_2O (2×30 mL) and brine (30 mL), dried (Na_2SO_4), concentrated, and purified by chromatography (silica gel,

150 mm×20 mm Ø, CH_2Cl_2/acetone 10:1) to yield product **27** (293 mg, 0.38 mmol, 68%) as a colorless foam.

*4.4.7. tert-Butyl (2S,2′S,2″R,1‴S)-2-(2-{2-[1-(benzyloxycarbonylamino)-2-methyl-propyl]-5-oxo-pyrrolidin-1-yl}-4-methylpentanamido)-3-phenylpropanoate (**32**).* TFA/H_2O (9:1, 1.1 mL) was added to *tert*-butyl ester **15** (170 mg, 1.00 mmol), the mixture was concentrated and the resulting carboxylic acid was used without further purification. Collidine (662 μL, 5.00 mmol) was added at 0 °C to a solution of the carboxylic acid (404 mg, 1.00 mmol), HATU (951 mg, 2.50 mmol), and H—Phe—O^{t}Bu (553 mg, 2.50 mmol) in DMF (5 mL). The mixture was stirred for 16 h, poured into H_2O (500 mL), and extracted with Et_2O (4×25 mL). The combined organic layers were washed with H_2O (2×30 mL) and brine (30 mL), dried (Na_2SO_4), concentrated, and purified (silica gel, 200 mm×25 mm Ø, CH_2Cl_2/acetone 10:1) to yield product **32** (474 mg, 0.78 mmol, 78%) as a colorless foam.

*4.4.8. tert-Butyl (2S,2′S,2″R)-2-{2-[2-(1-amino-2-methyl-propyl)-5-oxo-pyrrolidin-1-yl]-4-methyl-pentanoylamido}-3-phenyl-propanoate (**33**).* A suspension of carbamate **32** (395 mg, 0.65 mmol) and Pd/C (5%, 138 mg, 65 μmol) in anhydrous MeOH (5 mL) was stirred under a hydrogen atmosphere until completion of the hydrogenolysis (5 h, monitoring with TLC). The mixture was filtered (Celite), concentrated, and used for the peptide coupling without further purification as a colorless oil (308 mg, 0.65 mmol, quant.).

*4.4.9. tert-Butyl (2S,2′S,2″R,1‴S,2⁗S)-2-[2-(2-{1-[3-tert-butoxy-2-(9H-fluoren-9-ylmethoxycarbonylamino)-propionylamino]-2-methyl-propyl}-5-oxo-pyrrolidin-1-yl)-4-methyl-pentanoylamino]-3-phenyl-propanoate (**26**).* Collidine (242 μL, 221 mg, 1.82 mmol) was added at 0 °C to a solution of amine **33** (288 mg, 0.61 mmol), HATU (347 mg, 0.91 mmol), and Fmoc—Ser(O^{t}Bu)—OH (350 mg, 0.91 mmol) in DMF (5 mL). The mixture was stirred for 16 h, poured into H_2O (500 mL), and extracted with Et_2O (4×25 mL). The combined organic layers were washed with H_2O (2×30 mL) and brine (30 mL), dried (Na_2SO_4), concentrated, and purified by chromatography (silica gel, 150 mm×20 mm Ø, CH_2Cl_2/acetone 10:1) to yield product **26** (292 mg, 0.35 mmol, 57%) as a colorless foam.

4.5. Synthesis of pyrrolidine-derived peptidomimetics

*4.5.1. tert-Butyl (2S,2′S)-2-[2-(1-amino-2-methyl-propyl)-pyrrolidin-1-yl]-4-methyl-pentanoate (**34**).* A suspension of carbamate **19** (670 mg, 1.50 mmol) and Pd/C (5%, 319 mg, 0.15 mmol) in anhydrous MeOH (5 mL) was stirred under a hydrogen atmosphere until completion of the hydrogenolysis (5 h, monitoring with TLC). The mixture was filtered (Celite), concentrated, and used for the peptide coupling without further purification as a colorless oil (450 mg, 1.44 mmol, 96%).

*4.5.2. tert-Butyl (2S,2′S,1″S,2‴S)-2-(2-{1-[2-(9H-fluoren-9-ylmethoxycarbonylamino)-3-phenyl-propionylamino]-2-methyl-propyl}-pyrrolidin-1-yl)-4-methyl-pentanoate (**35**).* Collidine (270 μL, 251 mg, 2.07 mmol) was added at 0 °C to a solution of amine **34** (341 mg, 1.09 mmol), HATU (548 mg, 1.44 mmol), and Fmoc—Phe—OH (511 mg, 1.44 mmol) in DMF (5 mL). The mixture was stirred for 16 h, poured into H_2O (500 mL), and extracted with Et_2O (4×25 mL). The combined organic layers were washed with H_2O (2×30 mL) and brine (30 mL), dried (Na_2SO_4), concentrated, and purified by chromatography (silica gel, 200 mm×25 mm Ø, CH_2Cl_2/acetone 10:1) to yield product **35** (467 mg, 0.68 mmol, 63%) as a colorless foam.

*4.5.3. tert-Butyl (2S,2′S,2″S,1‴S,2⁗S)-2-[2-(2-{1-[2-(9H-fluoren-9-ylmethoxycarbonylamino)-3-phenyl-propionylamino]-2-methyl-propyl}-pyrrolidin-1-yl)-4-methyl-pentanoylamino]-propanoate (**28**).* TFA/H_2O (9:1, 2.2 mL) was added to *tert*-butyl ester **35** (261 mg, 0.38 mmol), the mixture was concentrated and the resulting carboxylic acid was used without further purification. Collidine (185 μL, 170 mg, 1.40 mmol) was added at 0 °C to a solution of the carboxylic acid (173 mg, 0.28 mmol), HATU (126 mg, 0.33 mmol), and H—Ala—O^{t}Bu (40 mg, 0.33 mmol) in DMF (5 mL). The mixture was stirred for 16 h, poured into H_2O (500 mL), and extracted with Et_2O (4×25 mL). The combined organic layers were washed with H_2O (2×30 mL) and brine (30 mL), dried (Na_2SO_4), concentrated, and purified (silica gel, 200 mm×25 mm Ø, CH_2Cl_2/acetone 10:1) to yield product **28** (102 mg, 0.14 mmol, 49%) as a colorless foam.

Supplementary data

Supplementary data for this article can be found in the online version, at doi:10.1016/j.tet.2010.05.099. These data include MOL files and InChIKeys of the most important compounds described in this article.

References and notes

1. (a) Smith, J. A.; Pease, L. G. *CRC Crit. Rev. Biochem. Mol. Biol.* **1980**, *8*, 315–399; (b) Richardson, J. S. In *Advances in Protein Chemistry*; Anfinsen, C. B., Edsall, J. T., Richards, F. M., Eds.; Academic: New York, NY, 1981; Vol. 34, 167–339; (c) Rose, G. D.; Gierasch, L. M.; Smith, J. A. In *Advances in Protein Chemistry*; Anfinsen, C. B., Edsall, J. T., Richards, F. M., Eds.; Academic: Orlando, 1985; Vol. 37, 1–109; (d) *Houben-Weyl, Synthesis of Peptides and Peptidomimetics, E22*; Goodman, M., Felix, A., Moroder, L., Toniolo, C., Eds.; Thieme: Stuttgart, 2001.
2. (a) Hallenga, K.; van Binst, G.; Scarso, A.; Michel, A.; Knappenberg, M.; Dremier, C.; Brison, J.; Dirkx, J. *FEBS Lett.* **1980**, *119*, 47–52; (b) Veber, D. F.; Freidinger, R. M.; Perlow, D. S.; Paleveda, W. J., Jr.; Holly, F. W.; Strachan, R. G.; Nutt, R. F.; Arison, B. H.; Homnick, C.; Randall, W. C.; Glitzer, M. S.; Saperstein, R.; Hirschmann, R. *Nature* **1981**, *292*, 55–58; (c) Rivier, J.; Spiess, J.; Thorner, M.; Vale, W. *Nature* **1982**, *300*, 276–278.
3. Urry, D. W.; Walter, R. *Proc. Natl. Acad. Sci. U.S.A.* **1971**, *68*, 956–958.
4. (a) Freidinger, R. M.; Veber, D. F.; Perlow, D. S.; Brooks, J. R.; Saperstein, R. *Science* **1980**, *210*, 656–658; (b) Ball, J. B.; Alewood, P. F. *J. Mol. Recognit.* **1990**, *3*, 55–64; (c) Kahn, M.; Eguchi, M. In *Houben-Weyl, Synthesis of Peptides and Peptidomimetics, E22*; Goodman, M., Felix, A., Moroder, L., Toniolo, C., Eds.; Thieme: Stuttgart, 2001; pp 695–740; (d) See as well: Müller, G.; Hessler, G.; Decornez, H. Y. *Angew. Chem., Int. Ed.* **2000**, *39*, 894–896.
5. Reviews: (a) Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789–12854; (b) Gillespie, P.; Cicariello, J.; Olson, G. L. *Biopolymers* **1997**, *43*, 191–217 β-, γ- and δ-lactam scaffolds; (c) Yu, K.-L.; Rajakumar, G.; Srivastava, L. K.; Mishra, R. K.; Johnson, R. L. *J. Med. Chem.* **1988**, *31*, 1430–1436; (d) Sreenivasan, U.; Mishra, R. K.; Johnson, R. L. *J. Med. Chem.* **1993**, *36*, 256–263; (e) Lehmann, T.; Michel, D.; Glänzel, M.; Waibel, R.; Gmeiner, P. *Heterocycles* **1999**, *51*, 1389–1400; (f) Hoffmann, T.; Lanig, H.; Waibel, R.; Gmeiner, P. *Angew. Chem., Int. Ed.* **2001**, *40*, 3361–3364; (g) Alonso, E.; López-Ortiz, F.; del Pozo, C.; Peralta, E.; Macías, A.; González, J. *J. Org. Chem.* **2001**, *66*, 6333–6338; (h) Dolbeare, K.; Pontoriero, G. F.; Gupta, S. K.; Mishra, R. K.; Johnson, R. L. *Bioorg. Med. Chem.* **2003**, *11*, 4103–4112; (i) Dolbeare, K.; Pontoriero, G. F.; Gupta, S. K.; Mishra, R. K.; Johnson, R. L. *J. Med. Chem.* **2003**, *46*, 727–733; (j) Galaud, F.; Lubell, W. D. *Biopolymers* **2005**, *80*, 665–674; (k) Broadrup, R. L.; Wang, B.; Malachowski, W. P. *Tetrahedron* **2005**, *61*, 10277–10284; (l) Seufert, W.; Fleury, A.; Giese, B. *Synlett* **2006**, 1774–1776; (m) Otvos, F.; Gembitsky, D. S.; Murphy, R. F.; Lovas, S. *Int. J. Pept. Res. Ther.* **2007**, *13*, 329–336; (n) Jamieson, A. G.; Boutard, N.; Beauregard, K.; Bodas Mandar, S.; Ong, H.; Quiniou, C.; Chemtob, S.; Lubell, W. D. *J. Am. Chem. Soc.* **2009**, *131*, 7917–7927; (o) Lesma, G.; Landoni, N.; Pilati, T.; Sacchetti, A.; Silvani, A. *J. Org. Chem.* **2009**, *74*, 8098–8105.
6. (a) Podlech, J. *Synlett* **1996**, 582–584; (b) Podlech, J.; Linder, M. R. *J. Org. Chem.* **1997**, *62*, 5873–5883; (c) Linder, M. R.; Podlech, J. *Org. Lett.* **2001**, *3*, 1849–1851; (d) Linder, M. R.; Frey, W. U.; Podlech, J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2566–2577; (e) Taubinger, A. A.; Fenske, D.; Podlech, J. *Synlett* **2008**, 539–542; (f) Taubinger, A. A.; Fenske, D.; Podlech, J. *Tetrahedron* **2008**, *64*, 8659–8667.
7. (a) Linder, M. R.; Podlech, J. *Org. Lett.* **1999**, *1*, 869–871; (b) Maier, T. C.; Frey, W. U.; Podlech, J. *Eur. J. Org. Chem.* **2002**, 2686–2689; (c) Maier, T. C.; Joachim Podlech, J. *Eur. J. Org. Chem.* **2004**, 4379–4386.
8. Virlouvet, M.; Goesmann, H.; Feldmann, C.; Podlech, J. *Monatsh. Chem.* **2010**, *141*, 177–198.
9. (a) Csuk, R.; Doerr, P. *J. Carbohydr. Chem.* **1995**, *14*, 35–44; (b) Clive, D. L. J.; Sun, S. *Tetrahedron Lett.* **2001**, *42*, 6267–6270.
10. Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019–8022.
11. du Vigneaud, V.; Ressler, C.; Swan, J. M.; Roberts, C. W.; Katsoyannis, P. G. *J. Am. Chem. Soc.* **1954**, *76*, 3115–3121.
12. Dong, H.-Q.; Lin, G.-Q. *Chin. Chem. Lett.* **1997**, *8*, 693–694.

13. (a) Lindsay, K. B.; Pyne, S. G. *Synlett* **2004**, 779–782; (b) Nannei, R.; Dallavalle, S.; Merlini, L.; Bava, A.; Nasini, G. *J. Org. Chem.* **2006**, *71*, 6277–6280.
14. Miller, R. D.; Goelitz, P. *J. Org. Chem.* **1981**, *46*, 1616–1618.
15. Davies, G.; Russell, A. T. *Tetrahedron Lett.* **2002**, *43*, 8519–8522.
16. Kim, Y. J.; Takatsuki, A.; Kogoshi, N.; Kitahara, T. *Tetrahedron* **1999**, *55*, 8353–8364.
17. Utilization of *N*-acyliminium intermediates in peptide chemistry has been reported: e.g., Nielsen, T. E.; Le Quement, S.; Meldal, M. *Org. Lett.* **2005**, *7*, 3601–3604.
18. Alexakis, A.; Tomassini, A.; Chouillet, C.; Roland, S.; Mangeney, S.; Bernardinelli, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 4093–4095.
19. Franke, F.; Guthrie, R. D. *Aust. J. Chem.* **1978**, *31*, 1285–1290.
20. Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1975**, *53*, 2975–2977.
21. Niwa, H.; Ito, S.; Hasegawa, T.; Wakamatsu, K.; Mori, T.; Yamada, K. *Tetrahedron Lett.* **1991**, *32*, 1329–1330.
22. (a) Carpino, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 4397–4398; (b) Pearson, A. J.; Chelliah, M. V.; Bignan, G. C. *Synthesis* **1997**, 536–540.
23. Gisin, B. F.; Merrifield, R. B. *J. Am. Chem. Soc.* **1972**, *94*, 3102–3106.
24. MM2 force field as implemented in ChemBio3D Ultra, Version 11.0.1, Cambridge Software corporation.
25. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.