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Synthesis of a β-strand mimetic based on a pyridine scaffold

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Abstract—A synthetic route to a 2,4-disubstituted pyridine as a potential β-strand mimetic has been developed and applied in the synthesis of a tripeptidomimetic of Leu-Gly-Gly. The pyridine scaffold replaces the central glycine, and is substituted with analogues of leucine and glycine in positions 4 and 2, respectively. 2-Fluoro-4-iodopyridine was chosen as the functionalized scaffold and was substituted with protected leucinal in position 4 via a Grignard exchange reaction using *iso*-propyl magnesium chloride. The glycine moiety was introduced in position 2 via a nucleophilic aromatic substitution reaction (S_NAr) facilitated by microwave irradiation. The synthetic sequence involved 12 steps with an overall yield of 7%.

1. Introduction

A β-strand is a saw-toothed arrangement where amino acid side chains alternate above and below a linear peptide backbone.[1] There are no intramolecular hydrogen bonds between the amino acids that make up a β-strand. However, by reversing the overall direction of the peptide backbone via a turn or a loop, a second β-strand may hydrogen bond to the first one, thereby initiating β-sheet formation. β-Strands are thus key elements in β-sheet secondary structures[2] and are also known to be important in protein–protein and protein–ligand interactions in various biological systems.[2]

Our research group is involved in studies of two systems where interactions between β-strands and proteins are crucial for the biological outcome. The molecular machinery of pilus assembly in uropathogenic *Escherichia coli* (UPEC) constitutes one system.[3,4] Adhesive pili, which are supramolecular protein appendages that anchor the UPEC to host tissue, are required for the pathogenicity of the bacterium. Such pili are formed through a highly conserved process called the chaperone/usher pathway, where interactions between β-strands are required both in the folding of pilus subunits and in the assembly of the subunits into functional pili.[3,4] Recently it was shown that peptides derived from β-strands of pilus subunits can inhibit the protein–protein interactions required for pilus assembly,[5] suggesting that β-strand mimetics may constitute leads for the development of a novel class of antibiotics targeting pilus assembly in UPECs.[6,7] The second system involves binding and presentation of a glycopeptide from type II collagen by major histocompatibility complex (MHC) molecules in an animal model for rheumatoid arthritis (RA).[8] This glycopeptide–MHC interaction has been found to be essential for the development of arthritis in mice, and further studies have shown that vaccination with the glycopeptide epitope has a protective effect.[9] A recent study identified the minimal, active glycopeptide epitope to consist of an octapeptide,[10] thereby setting the stage for developing β-strand mimetics as immunomodulators for treatment of RA.[11]

The important biological functions of peptides, together with their generally poor pharmacokinetic properties, make the development of peptidomimetics highly desirable. β-Strand mimetics have been developed by incorporation of a wide range of amide bond bioisosters,[2] including olefins[12] in the peptide backbone. Introduction of cyclic systems[13–17] to reduce flexibility and/or to induce extended conformations has also been used. Among cyclic systems, pyrrolinones have been particularly successful in retaining the biological activity of the original peptide.[15–17,18]

In this study a synthetic route to β-strand mimetics **2**, based on a 2,4-disubstituted pyridine scaffold (Fig. 1), has been developed. In mimetic **2**, which was designed using semiempirical and molecular mechanic calculations,[19] the pyridine scaffold replaces the central amino acid of a tripeptide sequence. Residues corresponding to the N-terminal and the C-terminal amino acids are attached at positions 4 and 2 of the pyridine ring, respectively.[19] As reported previously the scaffold permits introduction of a residue in position 3 of

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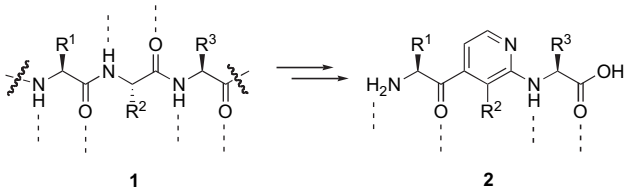


Figure 1. β-Strand mimetic **2**, which mimics tripeptide fragment **1**, was designed[19] based on a 2,4-disubstituted pyridine scaffold. Mimetic **2** lacks the two central amide bonds of tripeptide fragment **1**, but retains some of the hydrogen bonding capacity of **1**.

the pyridine ring, which corresponds to the side chain of the central amino acid of the tripeptide.[19,20] The two amide bonds have been replaced by a keto functionality at position 4 of the pyridine scaffold and by an amine at position 2, which thus serve as amide bioisosters. Additionally, the pyridine nitrogen atom is positioned with potential to mimic the carbonyl oxygen atom in the amide bond between the second and third residues of the original tripeptide. As a consequence of this modified hydrogen bonding pattern the β-strand mimetic maintains the ability to form hydrogen bonds with a complementary β-strand in one, but not in the other direction (Fig. 1).

2. Results and discussion

In order to establish the synthetic conditions that allow the synthesis of β-strand mimetics **2**, we choose Leu-Gly-Gly tripeptide mimetic **4** as our first target (Fig. 2). This requires the central pyridine scaffold to be substituted with a leucine and a glycine moiety in positions 4 and 2, respectively. Model compound **4** was thus chosen so as to contain a stereogenic center adjacent to the carbonyl group of the N-terminal moiety, while the C-terminal residue was kept simple at this stage. A retrosynthetic analysis revealed that mimetic **4** could be prepared from protected leucinal **5**, 2-fluoro-4-iodopyridine (**6**), and a glycine equivalent (**7**).

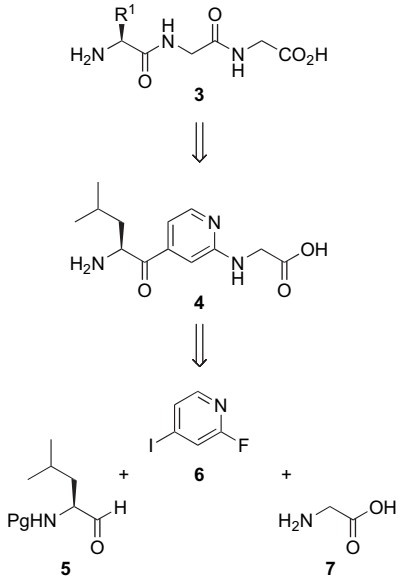
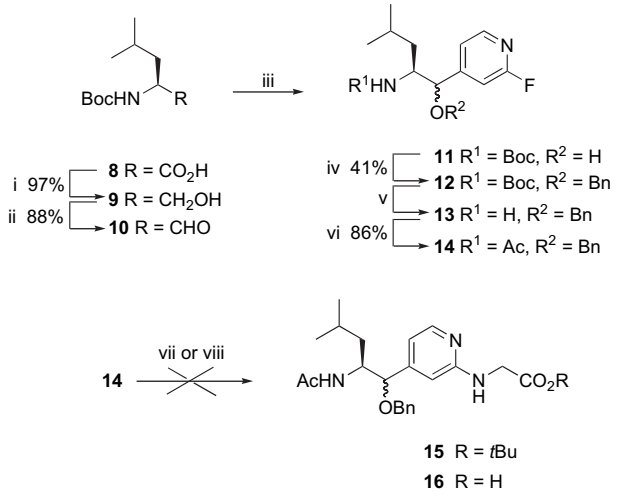


Figure 2. A retrosynthetic analysis suggests that β-strand mimetic **4** can be prepared from protected leucinal **5**, 2-fluoro-4-iodo-pyridine (**6**), and a glycine equivalent (**7**).

2-Fluoro-4-iodopyridine is a key building block and can be synthesized in two steps from 2-fluoropyridine.[21] The moiety in mimetic **4**, which corresponds to the leucine residue was intended to be introduced at position 4 of the pyridine scaffold via a Grignard exchange reaction[22] of the iodine atom with protected *S*-leucinal as electrophile.[20] Introduction of the glycine equivalent, which corresponds to the third amino acid of the tripeptide, was thereafter planned to be achieved by displacement of the fluorine atom of the scaffold via a nucleophilic aromatic substitution reaction (S_NAr).

The synthetic route started by reduction[23] of Boc-protected leucine **8** to alcohol **9** in 97% yield (Scheme 1). This was achieved via activation of the carboxyl group of **8** as a mixed anhydride using *iso*-butyl chloroformate, followed by reduction using sodium borohydride. Alcohol **9** was subsequently oxidized[24] to aldehyde **10** by treatment with Dess–Martin periodinane (88%). By keeping the product cold during work-up and continuing directly with the next step without further purification, epimerization of this sensitive intermediate was avoided.[25,26] In order to couple the central pyridine scaffold to aldehyde **10**, 2-fluoro-4-iodopyridine was treated with *iso*-propyl magnesium chloride at room temperature for 3 h to conduct a Grignard exchange reaction.[20] Addition of aldehyde **10** to the Grignard reagent then afforded alkylated pyridine **11** without affecting the fluorine atom in position 2 of the pyridine ring. Purification of alkylated pyridine **11** turned out to be more problematic than expected. Therefore, the alcohol functionality of crude **11** was directly protected as a benzyl ether under phase transfer conditions,[27] which allowed facile purification to give ether **12** (41% from **10**).

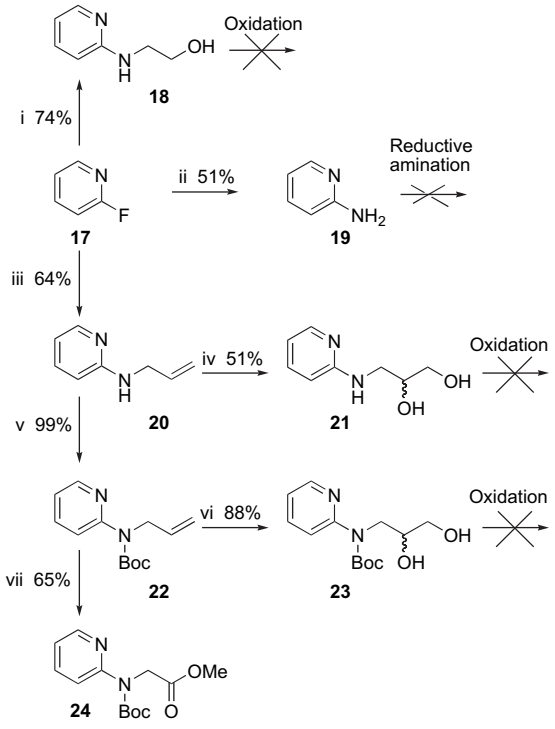


Scheme 1. Reagents and conditions: (i) NMM, *iso*-butyl chloroformate, $NaBH_4$, MeOH, THF, −15 °C, 97%; (ii) Dess–Martin periodinane, CH_2Cl_2, 88%; (iii) *iso*-PrMgCl, 2-fluoro-4-iodopyridine, THF; (iv) benzyl bromide, $QHSO_4$, 50% NaOH (aq), toluene, 41% from **10**; (v) formic acid; (vi) Ac_2O, DMAP, CH_2Cl_2, 86% from **12**; (vii) H_2N-Gly-O*t*Bu, pyridine, 150→180 °C; (viii) H_2N-Gly-OH, satd $NaHCO_3$ aq, 160 °C.

The C-terminal glycine moiety of the target β-strand mimetic was planned to be introduced by replacing the fluorine atom of **12** in an S_NAr reaction. In contrast to the substitution of 2-fluoropyridine analogues of **12** with oxygen nucleophiles, which has been accomplished under relatively mild conditions,[19,20] substitution of **12** with amines turned out

to be a significant challenge. Preferably the amino group of a glycine derivative would serve as a nucleophile in the substitution reaction. Initial attempts to accomplish this substitution resulted in partial cleavage of the Boc-group of **12**. The Boc-group was therefore removed using formic acid to give **13** and replaced by an acetyl group by treatment with acetic anhydride in dichloromethane to afford **14** (86% from **12**). As revealed by LCMS analysis, microwave irradiation of **14** at 150 °C for 1 h with glycine *tert*-butyl ester in pyridine gave the desired substitution product **15**, but only in trace amounts (appr. 1% yield). Raising the temperature to 180 °C did not increase the yield of **15**, instead this resulted in formation of a black solid in the reaction mixture, almost certainly by decomposition and polymerization of glycine *tert*-butyl ester. This was confirmed by running the same experiment without **14** present, which also resulted in a black solid. Based on the finding that the problems originated from the *tert*-butyl ester of glycine, substitution of **14** was attempted with unprotected glycine. In order to dissolve glycine, aqueous sodium hydrogen carbonate was used as solvent in the microwave assisted substitution reaction. When carried out at 160 °C for 1 h the desired product **16** was indeed obtained, but in an unsatisfactory yield (<10% according to LCMS) and accompanied by equal amounts of the product resulting from attack of water at position 2 of the pyridine ring.

In view of the difficulties encountered in the nucleophilic substitutions of **14** it was decided to study the reactions between 2-fluoropyridine (**17**) and various amines as model systems (Scheme 2). Just as for **14**, attempts to react glycine

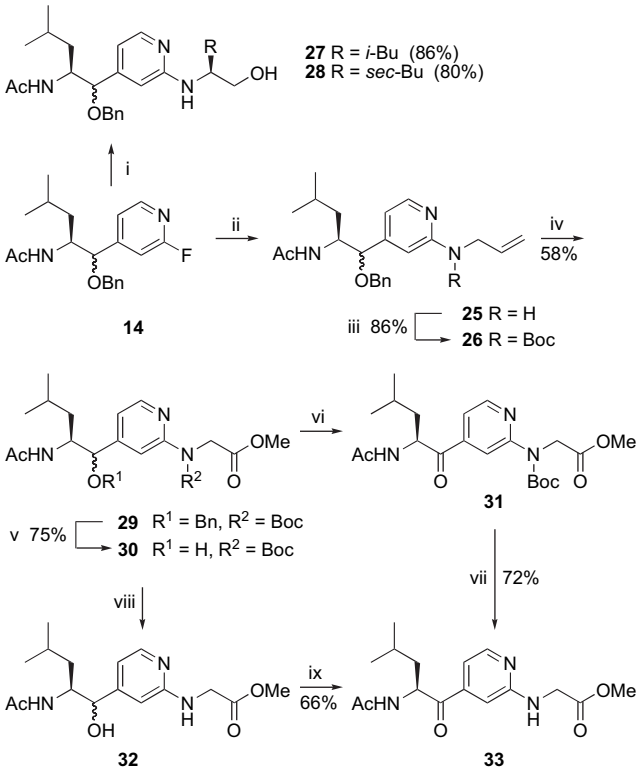


Scheme 2. Reagents and conditions: (i) ethanolamine, 2-fluoropyridine, pyridine, 210 °C, 74%; (ii) 25% NH_3 in H_2O, ~140 °C, 51%; (iii) allylamine, 2-fluoropyridine, pyridine, 190 °C, 64%; (iv) potassium osmate, NMO, H_2O, THF, acetone, 51%; (v) Boc_2O, DMAP, CH_2Cl_2, 99%; (vi) potassium osmate, NMO, H_2O, THF, acetone, 88%; (vii) NaOH (2 M in MeOH), CH_2Cl_2, O_3, −78 °C→rt, 65%.

or the *tert*-butyl ester of glycine with 2-fluoropyridine under different conditions using microwave irradiation failed; no reaction was observed with glycine while the *tert*-butyl ester of glycine polymerized into an insoluble black solid. Therefore, other glycine equivalents were explored as nucleophiles. Microwave irradiation of ethanolamine and 2-fluoropyridine in pyridine at 210 °C for 1 h gave derivative **18** (74%). Unfortunately, attempted oxidation of the alcohol functionality in **18** with Dess–Martin periodinane to give the corresponding aldehyde, or with ruthenium trichloride to the corresponding acid was unsuccessful. In an attempt to circumvent the problematic oxidation step, 2-fluoropyridine was converted to 2-aminopyridine[28] (**19**) by heating in 25% aqueous ammonia in a sealed steel cylinder. Anisaldehyde was then used to investigate different conditions for reductive amination of **19**. At best, a modest 36% yield could be obtained when sodium triacetoxyborohydride was used as the reducing agent in 1,2-dichloroethane under basic conditions.[29] Disappointingly, when these conditions were applied to reductive amination of 2-aminopyridine with glyoxylic acid, or with the more soluble *tert*-butyl glyoxylate[30] neither of the products were obtained.

Nucleophilic substitution of 2-fluoropyridine (**17**) was then investigated using allylamine as nucleophile, with the alkene part intended as a carboxylic acid precursor. Substitution was achieved by microwave irradiation of 2-fluoropyridine and allylamine in pyridine at 190 °C for 1 h to give substituted pyridine **20** (64%). Oxidation of the alkene moiety of **20** was accomplished by a catalytic amount of potassium osmate with *N*-methyl morpholine *N*-oxide as co-oxidant in a solvent mixture of water, tetrahydrofuran, and acetone to give diol **21** (51%). Further oxidation of diol **21** was first attempted with lead tetraacetate in toluene to give the corresponding aldehyde, and then with sodium periodate and bromine in methanol to give an ester functionality,[31] but neither of the desired products were obtained. Also, when direct oxidation[32] of the olefin in **20** to a methyl ester was attempted by ozonolytic cleavage in a mixture of methanolic sodium hydroxide and dichloromethane, all starting materials were consumed but no product was formed. To eliminate the possibility that the anilinic proton of **20** interferes during oxidation, aminopyridine **20** was protected[33] using Boc-anhydride and a catalytic amount of 4-dimethylaminopyridine to give derivative **22** (99%). Just as for **20** oxidation of **22** to diol **23** (88%) was successful, but again further oxidation of the diol failed. However, when Boc-protected aminopyridine **22** was treated with ozone in methanolic sodium hydroxide and dichloromethane,[34] the olefin was oxidized to give the desired ester **24** (65%).

Synthesis of the Leu-Gly-Gly β-strand mimetic from building block **14** was then brought to completion based on the learnings from the model study. Consequently, **14** was subjected to microwave irradiation in neat allylamine (2.5 h, 17 bar, ~150 °C) to give substituted pyridine **25** which, after aqueous work-up, was protected[33] with a Boc-group to afford protected 2-aminopyridine **26** (86% from **14**, Scheme 3). In order to investigate if more sterically demanding amino acid derivatives than the glycine equivalents ethanolamine and allylamine could be employed in the critical aromatic substitution of **14**, leucinol and *iso*-leucinol were chosen as nucleophiles. Building block **14** was first



Scheme 3. Reagents and conditions: (i) (a) leucinol, microwave irradiation 200 °C, to give **27**, 86%; (b) *iso*-leucinol, microwave irradiation 200–210 °C, to give **28**, 80%; (ii) allylamine, microwave irradiation (17 bar, ~150 °C); (iii) Boc_2O, DMAP, CH_2Cl_2, 86% from **14**; (iv) NaOH (2 M in MeOH), CH_2Cl_2, O_3, −78 °C→rt, 58%; (v) Pd/C, H_2 (1 atm), MeOH, AcOH, 75%; (vi) Dess–Martin periodinane, CH_2Cl_2; (vii) formic acid, 72% from **30**; (viii) 25% TFA in CH_2Cl_2; (ix) Dess–Martin periodinane, CH_2Cl_2, 66% from **30**.

dissolved in leucinol (appr. 20 equiv) and heated to 200 °C by microwave irradiation, which afforded substituted pyridine **27** (86%). Encouraged by this result, the even more sterically hindered *iso*-leucinol was used as nucleophile and gave the desired compound **28** (80%) when heating to 210 °C. Further attempts to convert derivatives **27** and **28**, or analogues thereof, into more complex β-strand mimetics will be the subject of future studies. Instead the synthetic sequence continued with oxidation of the olefinic part of **26** to methyl ester **29** (58%) by ozonolytic cleavage in basic methanolic solution.[32] Careful adjustment of the reaction time was necessary to avoid oxidation of the benzyl ether in **29** to an undesired benzoyl ester. Thereafter the benzyl ether of **29** was removed by hydrogenolysis in a mixture of methanol and acetic acid to give **30** (75%). Oxidation to ketone **31** using Dess–Martin periodinane followed by removal of the Boc-protective group afforded the desired β-strand mimetic **33** (72% from **30**). Somewhat surprisingly, chiral chromatography of mimetic **33** on a silica based column, revealed that partial epimerization (~60% ee) of the chiral center of **33** had occurred. However, ketone **31**, the direct precursor of **33**, was found to be enantiomerically pure as determined by chiral chromatography. It was therefore concluded that cleavage of the Boc-group of pure **31**, under acidic conditions had caused the epimerization via enolization of the ketone. To circumvent this problem, acidic removal of the Boc-group was performed already on alcohol **30** using trifluoroacetic acid (25%) in dichloromethane to give amine **32**. Finally, oxidation of the alcohol moiety of **32** using Dess–Martin periodinane gave β-strand mimetic **33** (66% from **30**) in enantiomerically pure form according to chiral chromatography. In conclusion, the synthesis of β-strand mimetic **33** was accomplished in a 12-step synthetic sequence with an overall yield of 7%.

3. Experimental

3.1. General

^1H NMR and ^{13}C NMR were recorded in $CDCl_3$ or in CD_3OD at 298 K. ^1H NMR and ^{13}C NMR signals are assigned with support from appropriate 2D-NMR and are presented in Supplementary data. For compounds that contain an uneven mixture of diastereomers (**12**–**14** and **25**–**30**), only signals for the major diastereomer are assigned. All microwave irradiations were performed in a Smithcreator with Emrys™ process vials (2–5 mL for compounds **18**, **20**, and **25**, or 0.5–1.5 mL for compounds **27** and **28**), temperature and pressure measurements were performed by infrared detection. Chiral HPLC was run on a Pirkle covalent (*S*,*S*) whelk-O1 10/100 Krom FCC, with heptane/CH_2Cl_2/2-propanol 48:48:4 for compounds **33** and **33***rac*, 49:49:2 for compounds **31** and **31***rac* as eluent. Chromatograms of both **33** and **33***rac* are presented in Supplementary data.

3.2. Procedures

3.2.1. *tert*-Butyl [(1*S*)-1-(hydroxymethyl)-3-methylbutyl]carbamate (9). Boc-Leu-OH·H_2O (**8**, 7.0 g, 28 mmol) was evaporated from toluene and dissolved in THF (80 mL). *N*-Methyl morpholine (3.3 mL, 29 mmol) was added and the reaction was cooled to −20 °C. The reaction was treated with *iso*-butyl chloroformate (4.4 mL, 29 mmol) and stirred for 30 min. The formed precipitate was removed by filtration and rinsed with THF (30 mL). To the clear filtrate $NaBH_4$ (3.2 g, 84 mmol) was added in one portion followed by careful addition of methanol (200 mL) at −20 °C. After 1 h the reaction was quenched with satd NH_4Cl aq followed by addition of EtOAc. The two phases were separated and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel pretreated with triethylamine) EtOAc/heptane 1:4→1:2 to give alcohol **9** (5.9 g, 97%) as a clear oil; $[\alpha]_D^{20}$ −25.8 (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 4.62 (d, J=8.0 Hz, 1H), 3.76–3.59 (m, 2H), 3.53–3.44 (m, 1H), 2.72 (s, 1H), 1.71–1.59 (m, 1H), 1.43 (s, 9H), 1.34–1.25 (m, 2H), 0.92 (d, J=1.7 Hz, 3H), 0.91 (d, J=1.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 79.6, 66.5, 51.0, 40.5, 28.4, 24.8, 23.0, 22.2; IR (neat): 3590–3138, 1688, 1529 cm^{-1}; FABHRMS calcd for $C_{11}H_{24}NO_3$ (M+H): 218.1756, found: 218.1756.

3.2.2. *tert*-Butyl [(1*S*)-1-formyl-3-methylbutyl]carbamate (10). Alcohol **9** (0.11 g, 0.51 mmol) was dissolved in CH_2Cl_2 (3 mL) and treated with Dess–Martin periodinane in CH_2Cl_2 (1.6 mL, 15 wt % in CH_2Cl_2, 0.76 mmol). After 1 h a white precipitate was formed and sodium bisulfite (1.0 g, 5.3 mmol) in satd $NaHCO_3$ aq was added. The organic layer was washed with satd $NaHCO_3$ aq, dried

over Na_2SO_4, and concentrated under reduced pressure at 0 °C to give aldehyde **10** (96 mg, 88%) as a clear oil, which was used without further purification for the next step.

3.2.3. *tert*-Butyl {(1*S*)-1-[(*RS*)-(benzyloxy)(2-fluoropyridin-4-yl)methyl]-3-methylbutyl}carbamate (12). 2-Fluoro-4-iodopyridine (1.2 g, 5.4 mmol) and *iso*-propyl magnesium chloride (2.6 mL, 5.5 mmol) was stirred in THF (2 mL) for 3 h. To this solution aldehyde **10** (0.56 g, 2.6 mmol) dissolved in THF (2 mL) was added and the mixture was stirred for another 15 h. The reaction was quenched with satd NH_4Cl aq followed by addition of satd $NaHCO_3$ aq and brine and extraction with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. To the residue toluene (40 mL) and NaOH aq (50%, 30 mL) were added. The vigorously stirred two phase system was treated with benzyl bromide (0.31 mL, 2.8 mmol) and tetrabutylammonium hydrogen sulfate (0.10 g, 0.30 mmol). After 3 h water was added followed by extraction with Et_2O. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography EtOAc/heptane 1:9→1:4 to give **12** (0.43 g, 41%) as a clear oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J=5.1 Hz, 1H), 7.40–7.27 (m, 5H), 7.12 (d, J=5.1 Hz, 1H), 6.92 (s, 1H), 4.60 (d, J=9.9 Hz, 1H), 4.56 (d, J=12 Hz, 1H), 4.43 (d, J=1.7 Hz, 1H), 4.32 (d, J=12 Hz, 1H), 3.94–3.85 (m, 1H), 1.64–1.51 (m, 1H), 1.44–1.36 (m, 2H), 1.30 (s, 9H), 0.91 (d, J=6.6 Hz, 3H), 0.89 (d, J=6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0 (d, J_{C-F}=239 Hz), 155.1, 147.5 (d, J_{C-F}=15 Hz), 137.1, 128.5, 128.1, 128.0, 119.9, 107.7 (d, J_{C-F}=37 Hz), 80.5, 79.3, 71.8, 53.2, 41.2, 28.2, 24.7, 23.0, 22.1; IR (neat): 1703, 1612 cm^{-1}; FABHRMS calcd for $C_{23}H_{32}FN_2O_3$ (M+H): 403.2397, found: 403.2389.

3.2.4. *N*-{(1*S*)-1-[(*RS*)-(Benzyloxy)(2-fluoropyridin-4-yl)-methyl]-3-methylbutyl}acetamide (14). Boc-protected amine **12** (0.31 g, 0.77 mmol) was treated with formic acid (12 mL) for 3 h. Formic acid was removed under reduced pressure and the residue was dissolved in EtOAc and washed with satd $NaHCO_3$ aq and the aqueous phase was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (7.5 mL) followed by addition of acetic anhydride (0.08 mL, 0.86 mmol) and 4-dimethylaminopyridine (0.1 g, 0.82 mmol). After 2 h a 1:3 mixture of satd $NaHCO_3$ aq and brine was added and the two phases were separated and the aqueous layer was extracted with EtOAc. The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography EtOAc/heptane 3:2 to give **14** (0.23 g, 86%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J=5.2 Hz, 1H), 7.41–7.28 (m, 5H), 7.10 (d, J=5.2 Hz, 1H), 6.88 (s, 1H), 5.53 (d, J=9.7 Hz, 1H), 4.57 (d, J=11 Hz, 1H), 4.47 (d, J=2.7 Hz, 1H), 4.34 (d, J=11 Hz, 1H), 4.31–4.23 (m, 1H), 1.85 (s, 3H), 1.55–1.46 (m, 1H), 1.45–1.39 (m, 2H), 0.91 (d, J=6.5 Hz, 3H), 0.89 (d, J=6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 164.0 (d, J_{C-F}=237 Hz), 154.9 (d, J_{C-F}=7 Hz), 147.6 (d, J_{C-F}=15 Hz), 136.9, 128.6, 128.3, 128.1, 119.7 (d, J_{C-F}=4 Hz), 107.5 (d, J_{C-F}= 38 Hz), 80.0, 72.0, 51.7, 41.1, 24.8, 23.1, 23.0, 22.2; IR (neat): 1652, 1552 cm^{-1}; FABHRMS calcd for $C_{20}H_{26}FN_2O_2$ (M+H): 345.1978, found: 345.1977.

3.2.5. 2-(Pyridin-2-ylamino)ethanol (18). 2-Fluoropyridine (0.3 mL, 3.5 mmol) was dissolved in pyridine (1 mL) and ethanolamine (2.1 mL, 35 mmol). The reaction was subjected to microwave irradiation at 210 °C for 1 h. Satd $NaHCO_3$ aq and EtOAc were added to the reaction and the two phases were separated. The aqueous layer was extracted with EtOAc and CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure to give alcohol **18** (0.36 g, 74%) as a colorless amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02–7.97 (m, 1H), 7.34 (ddd, J=9.2, 7.1, and 1.9 Hz, 1H), 6.57–6.52 (m, 1H), 6.42 (d, J=8.4 Hz, 1H), 5.06 (br s, 1H), 4.92 (br s, 1H), 3.77 (t, J=4.8 Hz, 2H), 3.49–3.42 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 147.1, 137.5, 112.9, 108.3, 63.0, 45.2; IR (neat): 3347–3132, 1607, 1524 cm^{-1}; FABHRMS calcd for $C_7H_{11}N_2O$ (M+H): 139.0871, found: 139.0878.

3.2.6. Allyl-pyridin-2-yl-amine (20). Allylamine (0.79 mL, 10.5 mmol) and 2-fluoropyridine (0.3 mL, 3.5 mmol) were dissolved in pyridine (2 mL) and subjected to microwave irradiation to 190 °C for 1 h. The reaction mixture was concentrated under reduced pressure and purified by flash chromatography EtOAc/heptane 2:1 to give aminopyridine **20** (0.3 g, 64%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09–8.05 (m, 1H), 7.39 (ddd, J=8.8, 7.1, and 1.9 Hz, 1H), 6.55 (ddd, J=7.1, 5.1, and 0.9 Hz, 1H), 6.37 (d, J=8.8 Hz, 1H), 5.99–5.88 (m, 1H), 5.28–5.22 (m, 1H), 5.16–5.11 (m, 1H), 4.78 (br s, 1H), 3.94–3.89 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 148.1, 137.3, 135.0, 115.8, 112.9, 106.6, 44.6; IR (neat): 3371–3178, 1601, 1571, 1510 cm^{-1}; FABHRMS calcd for $C_8H_{11}N_2$ (M+H): 135.0922, found: 135.0932.

3.2.7. 3-(Pyridin-2-ylamino)propane-1,2-diol (21). Alkene **20** (0.12 g, 0.92 mmol) was dissolved in H_2O (5.5 mL), acetone (5.5 mL), and THF (5.5 mL). Potassium osmate(VI) dihydrate (5 mg, 14 μmol) and *N*-methyl morpholine *N*-oxide (0.23 g, 1.96 mmol) were added and the reaction was stirred for 15 h. The solvents were removed under reduced pressure with toluene as azeotrope. The residue was purified by flash chromatography EtOH/toluene 1:6 to give diol **21** (0.78 g, 51%) as a colorless amorphous solid; ^{1}H NMR (400 MHz, CD_3OD) δ 7.92–7.87 (m, 1H), 7.41 (ddd, J=9.2, 7.0, and 1.9 Hz, 1H), 6.58–6.51 (m, 2H), 3.80–3.72 (m, 1H), 3.53 (d, J=5.6 Hz, 2H), 3.45 (dd, J=14.1 and 4.6 Hz, 1H), 3.32 (dd, J=14.1 and 6.3 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 160.6, 147.5, 138.8, 113.4, 110.2, 72.7, 64.8, 45.6; IR (neat): 3292, 1611, 1575 cm^{-1}; FABHRMS calcd for $C_8H_{13}N_2O_2$ (M+H): 169.0977, found: 169.0984.

3.2.8. *tert*-Butyl allyl(pyridin-2-yl)carbamate (22). Aminopyridine **20** (55 mg, 0.41 mmol) was dissolved in CH_2Cl_2 (2.5 mL) and treated with di-*tert*-butyl dicarbonate (0.19 g, 0.86 mmol) and a catalytic amount of 4-dimethylaminopyridine (5 mg, 41 μmol). After 15 h satd $NaHCO_3$ aq was added and the two phases were separated. The aqueous phase was extracted with CH_2Cl_2 and the combined organic phases were dried over Na_2SO_4 and concentrated under

reduced pressure. The residue was purified by flash chromatography EtOAc/heptane 1:7 to give Boc-protected aminopyridine **22** (96 mg, 99%) as a clear oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38–8.34 (m, 1H), 7.67–7.57 (m, 2H), 7.01–6.96 (m, 1H), 6.00–5.89 (m, 1H), 5.18–5.06 (m, 2H), 4.58–4.53 (m, 2H), 1.50 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 154.2, 147.7, 136.9, 134.8, 119.6, 119.4, 115.8, 81.2, 49.2, 28.3; IR (neat): 1706, 1650, 1588, 1551 cm^{-1}; FABHRMS calcd for $C_{13}H_{19}N_2O_2$ (M+H): 235.1447, found: 235.1447.

3.2.9. *tert*-Butyl (2,3-dihydroxypropyl)pyridin-2-ylcarbamate (23). Boc-protected aminopyridine **22** (96 mg, 0.41 mmol) was dissolved in H_2O (2.5 mL), acetone (2.5 mL), and THF (2.5 mL). Potassium osmate(VI) dihydrate (5 mg, 14 μmol) and *N*-methyl morpholine *N*-oxide (0.10 g, 0.88 mmol) were added and the reaction was stirred for 15 h. Brine, satd $NaHCO_3$, and EtOAc were added and the two phases were separated. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography EtOAc/heptane 2:1 to give diol **23** (97 mg, 88%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29–8.25 (m, 1H), 7.69–7.63 (m, 1H), 7.59–7.54 (m, 1H), 7.08–7.03 (m, 1H), 4.01–3.91 (m, 2H), 3.87–3.79 (m, 1H), 3.64 (dd, *J*=12 and 4.8 Hz, 1H), 3.58 (dd, *J*=12 and 4.8 Hz, 1H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 153.9, 146.4, 137.7, 120.3, 120.1, 82.2, 70.6, 64.1, 51.2, 28.1; IR (neat): 3605–3064, 1705, 1594, 1572 cm^{-1}; FABHRMS calcd for $C_{13}H_{21}N_2O_4$ (M+H): 269.1501, found: 269.1494.

3.2.10. (*tert*-Butoxycarbonyl-pyridin-2-yl-amino)-acetic acid methyl ester (24). Boc-protected aminopyridine **22** (0.10 g, 0.44 mmol) was dissolved in CH_2Cl_2 (3.5 mL) and a 2 M solution of NaOH in methanol (0.90 mL) and cooled to −78 °C. O_3 was passed through the solution, which turned bright yellow at first and gradually decolorized. A colorless precipitate was formed and the solution turned blue and the excess of O_3 was purged from the solution with a stream of oxygen. Water and Et_2O were added and the two phases were separated and the aqueous layer was extracted with EtOAc. The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure to give ester **24** (75 mg, 65%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30–8.27 (m, 1H), 7.83 (br d, *J*=8.6 Hz, 1H), 7.62 (ddd, *J*=8.6, 7.3, and 1.9 Hz, 1H), 6.97 (ddd, *J*=7.3, 4.9, and 0.9 Hz, 1H), 4.71 (s, 2H), 3.73 (s, 3H), 1.50 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 153.5, 153.5, 147.1, 137.0, 119.2, 118.2, 82.0, 51.9, 47.7, 28.1; IR (neat): 1758, 1720, 1590 cm^{-1}; FABHRMS calcd for $C_{13}H_{19}N_2O_4$ (M+H): 267.1345, found: 267.1344.

3.2.11. *tert*-Butyl{4-[(1*RS*,2*S*)-2-(acetylamino)-1-(benzyloxy)-4-methylpentyl]pyridin-2-yl}allylcarbamate (26). Fluoropyridine **14** (0.23 g, 0.66 mmol) was dissolved in allylamine (4 mL) and subjected to microwave irradiation to 17 bar (~150 °C) for 2.5 h. Allylamine was removed under reduced pressure and the residue was dissolved in CH_2Cl_2, followed by addition of a 1:3 mixture of satd $NaHCO_3$ aq and brine. The two phases were separated and the aqueous layer was extracted with EtOAc. The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (15 mL) and treated with di-*tert*-butyl dicarbonate (0.36 g, 1.65 mmol) and 4-dimethylaminopyridine (0.01 g, 0.082 mmol). After 20 h a 1:3 mixture of satd $NaHCO_3$ aq and brine was added and the two phases were separated. The aqueous layer was extracted with EtOAc and the combined organic phases were dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash chromatography EtOAc/heptane 1:1 to give **26** (0.27 g, 86%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J*=5.1 Hz, 1H), 7.62 (s, 1H), 7.40–7.29 (m, 5H), 6.98 (dd, *J*=5.1 and 1.1 Hz, 1H), 6.03–5.92 (m, 1H), 5.52 (d, *J*=9.5 Hz, 1H), 5.16 (dd, *J*=17 and 1.6 Hz, 1H), 5.10 (dd, *J*=10 and 1.6 Hz, 1H), 4.59 (d, *J*=12 Hz, 1H), 4.56–4.52 (m, 2H), 4.47 (d, *J*=2.4 Hz, 1H), 4.37 (d, *J*=12 Hz, 1H), 4.35–4.27 (m, 1H), 1.91 (s, 3H), 1.51 (s, 9H), 1.49–1.41 (m, 1H), 1.32–1.24 (m, 2H), 0.91 (d, *J*=2.7 Hz, 3H), 0.89 (d, *J*=2.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 154.4, 154.1, 149.2, 147.4, 137.6, 134.8, 128.5, 128.1, 128.0, 117.6, 115.8, 81.1, 80.5, 71.7, 51.4, 49.1, 40.4, 28.3, 24.7, 23.2, 23.1, 22.2; IR (neat): 1704, 1650, 1601, 1555 cm^{-1}; FABHRMS calcd for $C_{28}H_{40}N_3O_4$ (M+H): 482.3019, found: 482.3023.

3.2.12. {4-[(1*RS*,2*S*)-2-(Acetylamino)-1-(benzyloxy)-4-methylpentyl]pyridin-2-ylamino}-*S*-leucinol (27). Fluoropyridine **14** (0.18 g, 0.53 mmol) was dissolved in *S*-leucinol (1.2 mL, 9.3 mmol) and heated by microwave irradiation (200 °C, 90 min). The reaction mixture was put on a silica gel column and eluted with EtOH/toluene 1:15→1:8 to give **27** (0.20 g, 86%) as a white foam; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J*=5.3 Hz, 1H), 7.38–7.26 (m, 5H), 6.49 (d, *J*=5.3 Hz, 1H), 6.38 (s, 1H), 5.70 (d, *J*=9.4 Hz, 1H), 4.76 (d, *J*=6.9 Hz, 1H), 4.55 (d, *J*=11.7 Hz, 1H), 4.31 (d, *J*=11.7 Hz, 1H), 4.29 (d, *J*=3.2 Hz, 1H), 4.28–4.20 (m, 1H), 3.88–3.80 (m, 1H), 3.71 (dd, *J*=11 and 3.2 Hz, 1H), 3.49 (dd, *J*=11 and 6.6 Hz, 1H), 1.86 (s, 3H), 1.77–1.67 (m, 1H), 1.55–1.45 (m, 1H), 1.43–1.36 (m, 4H), 0.97–0.85 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 158.9, 149.9, 147.0, 137.5, 128.3, 127.9, 127.8, 111.3, 106.1, 80.5, 71.5, 67.1, 52.7, 51.6, 41.0, 40.6, 24.9, 24.7, 23.1, 23.0, 22.9, 22.4, 22.1; IR (neat): 3371–3129, 1649, 1620, 1560 cm^{-1}; FABHRMS calcd for $C_{26}H_{40}N_3O_3$ (M+H): 442.3070, found: 442.3069.

3.2.13. {4-[(1*RS*,2*S*)-2-(Acetylamino)-1-(benzyloxy)-4-methylpentyl]pyridin-2-ylamino}-*S*-*iso*-leucinol (28). Fluoropyridine **14** (0.10 g, 0.30 mmol) was dissolved in *S*-*iso*-leucinol (1.1 g, 9.2 mmol) and heated by microwave irradiation (200 °C, 90 min and 210 °C, 30 min). The reaction mixture was put on a silica column and eluted with EtOH/toluene 1:15→1:10 to give **28** (0.11 g, 80%) as a white foam; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J*=5.2 Hz, 1H), 7.37–7.27 (m, 5H), 6.49 (dd, *J*=5.2 and 1.1 Hz, 1H), 6.38 (s, 1H), 5.73 (d, *J*=9.7 Hz, 1H), 4.92 (d, *J*=7.0 Hz, 1H), 4.55 (d, *J*=12 Hz, 1H), 4.31 (d, *J*=12 Hz, 1H), 4.29 (d, *J*=3.2 Hz, 1H), 4.28–4.20 (m, 1H), 3.75 (d, *J*=8.7 Hz, 1H), 3.63–3.55 (m, 2H), 1.86 (s, 3H), 1.74–1.64 (m, 1H), 1.58–1.46 (m, 2H), 1.42–1.35 (m, 2H), 1.26–1.15 (m, 1H), 0.97–0.86 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 159.1, 149.9, 147.1, 137.5, 128.3, 127.8, 127.8, 111.1, 106.1, 80.5, 71.4, 64.1, 58.8, 51.6, 40.5, 36.8, 25.8, 24.7, 23.0, 23.0, 22.1, 15.4, 11.6; IR (neat): 3474–3117,

1649, 1609, 1561, 1516 cm^{-1}; FABHRMS calcd for $C_{26}H_{40}N_3O_3$ (M+H): 442.3070, found: 442.3066.

3.2.14. Methyl *N*-{4-[(1*RS*,2*S*)-2-(acetylamino)-1-(benzyloxy)-4-methylpentyl]pyridin-2-yl}-*N*-(*tert*-butoxycarbonyl)glycinate (29). Olefin **26** (0.27 g, 0.57 mmol) was dissolved in CH_2Cl_2 (10 mL) and a solution of 2 M NaOH in methanol (0.56 mL) and cooled to −78 °C. O_3 was passed through the solution, which turned bright yellow at first and was decolorized gradually. A colorless solid was formed and the solution turned light blue and the excess of O_3 was purged from the solution with a stream of oxygen. Water and Et_2O were added and the two phases were separated and the aqueous layer was extracted with EtOAc. The combined organic phases were dried over Na_2SO_4, concentrated under reduced pressure, and the residue was purified by flash chromatography EtOAc/heptane 3:2 to give **29** (0.17 g, 58%) as a colorless amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J=5.1 Hz, 1H), 7.80 (s, 1H), 7.40–7.28 (m, 5H), 6.98 (d, J=5.1 Hz, 1H), 5.53 (d, J=9.8 Hz, 1H), 4.75 (d, J=18 Hz, 1H), 4.67 (d, J=18 Hz, 1H), 4.58 (d, J=11 Hz, 1H), 4.47 (d, J=2.7 Hz, 1H), 4.36 (d, J=11 Hz, 1H), 4.34–4.25 (m, 1H), 3.75 (s, 3H), 1.92 (s, 3H), 1.51 (s, 9H), 1.49–1.41 (m, 1H), 1.34–1.23 (m, 2H), 0.93 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 169.6, 153.6, 153.5, 149.5, 147.1, 137.5, 128.4, 128.1, 127.9, 117.5, 116.5, 82.0, 80.5, 71.6, 52.0, 51.4, 47.8, 40.4, 28.1, 24.7, 23.2, 23.1, 22.1; IR (neat): 1754, 1715, 1655, 1602 cm^{-1}; FABHRMS calcd for $C_{28}H_{40}N_3O_6$ (M+H): 514.2917, found: 514.2917.

3.2.15. Methyl *N*-{4-[(1*RS*,2*S*)-2-(acetylamino)-1-hydroxy-4-methylpentyl]pyridin-2-yl}-*N*-(*tert*-butoxycarbonyl)glycinate (30). Benzyl protected alcohol **29** (0.16 g, 0.30 mmol) and Pd/C (0.15 g) were added to a mixture of MeOH (15 mL) and AcOH (0.15 mL). The reaction was stirred vigorously under H_2 atmosphere (1 atm) for 30 h. Pd/C was removed by filtration through Celite and the solvent was removed under reduced pressure. The residue was purified by flash chromatography EtOAc/heptane 2:1 → 1:0 to give **30** (0.096 g, 75%) as a colorless amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J=5.2 Hz, 1H), 7.75 (s, 1H), 7.01 (d, J=5.2 Hz, 1H), 5.73 (d, J=9.1 Hz, 1H), 4.74–4.67 (m, 1H), 4.69 (s, 2H), 4.16–4.06 (m, 1H), 3.92 (s, 1H), 3.74 (s, 3H), 1.94 (s, 3H), 1.67–1.57 (m, 1H), 1.51 (s, 9H), 1.45–1.37 (m, 2H), 0.92 (d, J=2.3 Hz, 3H), 0.90 (d, J=2.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 170.7, 153.6, 153.4, 152.1, 147.1, 117.1, 115.7, 82.1, 74.7, 53.5, 52.0, 47.8, 39.5, 28.1, 24.8, 23.2, 23.1, 21.9; IR (neat): 3280, 3254, 1713, 1607, 1603, 1529 cm^{-1}; FABHRMS calcd for $C_{21}H_{34}N_3O_6$ (M+H): 424.2448, found: 424.2457.

3.2.16. (2*S*)-{[4-(2-Acetylamino-4-methyl-pentanoyl)-pyridin-2-yl]-*tert*-butoxycarbonyl-amino}-acetic acid methyl ester (31). Alcohol **30** (96 mg, 0.23 mmol) was dissolved in CH_2Cl_2 (3 mL) and treated with Dess–Martin periodinane (0.80 mL, 15 wt % in CH_2Cl_2, 0.34 mmol) for 20 min. Sodium disulfite (0.49 g, 2.55 mmol) in satd $NaHCO_3$ aq was added and the two phases were separated and the aqueous phase was extracted with EtOAc followed by a wash with satd $NaHCO_3$ aq. The organic layer was dried over Na_2SO_4, concentrated under reduced pressure, and purified by flash chromatography EtOAc/heptane 3:1 to give ketone **31** (77 mg, 81%) as a colorless oil; $[\alpha]_D^{20}$ +4.4 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (dd, J=5.1 and 0.6 Hz, 1H), 8.40 (s, 1H), 7.44 (dd, J=5.1 and 1.5 Hz, 1H), 6.13 (d, J=8.2 Hz, 1H), 5.61–5.54 (m, 1H), 4.74 (s, 2H), 3.75 (s, 3H), 2.05 (s, 3H), 1.79–1.59 (m, 2H), 1.53 (s, 9H), 1.46–1.36 (m, 1H), 1.07 (d, J=6.5 Hz, 3H), 0.89 (d, J=6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.3, 170.3, 169.8, 154.9, 153.2, 148.3, 142.2, 116.5, 116.5, 82.7, 53.0, 52.1, 47.7, 42.1, 28.1, 25.2, 23.3, 23.2, 21.6; IR (neat): 1753, 1709, 1652, 1598, 1554 cm^{-1}; FABHRMS calcd for $C_{21}H_{32}N_3O_6$ (M+H): 422.2291, found: 422.2298.

3.2.17. (2*R*,*S*)-{[4-(2-Acetylamino-4-methyl-pentanoyl)-pyridin-2-yl]-*tert*-butoxycarbonyl-amino}-acetic acid methyl ester (31*rac*). Prepared in the same way as **33***rac* starting with compound **31** (4 mg, 9.5 μmol) to give **31***rac* (3 mg, 75%) as determined by chiral HPLC; $[\alpha]_D^{20}$ 0 (*c* 0.25, $CHCl_3$); ^{1}H NMR identical as for compound **31**.

3.2.18. (2*S*)-[4-(2-Acetylamino-4-methyl-pentanoyl)-pyridin-2-ylamino]-acetic acid methyl ester (33). Boc-protected amine **30** (28 mg, 66 μmol) was dissolved in CH_2Cl_2 (6 mL) and treated with trifluoroacetic acid (2 mL) for 1.5 h. The reaction mixture was concentrated under reduced pressure and coevaporated from $CHCl_3$. The residue was dissolved in CH_2Cl_2 and treated with Dess–Martin periodinane (0.22 mL, 15 wt % in CH_2Cl_2, 99 μmol). After 4 min sodium bisulfite (0.19 g, 0.97 mmol) in satd $NaHCO_3$ aq was added. The organic layer was washed with satd $NaHCO_3$ aq, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography EtOAc/heptane 2:1 → 4:1 to give β-strand mimetic **33** (0.014 g, 66%) as a yellow oil. $[\alpha]_D^{20}$ +11.5 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J=5.2 Hz, 1H), 7.03 (d, J=5.2 Hz, 1H), 6.98 (s, 1H), 6.27 (d, J=8.1 Hz, 1H), 5.55–5.46 (m, 1H), 5.35 (t, J=5.5 Hz, 1H), 4.19 (d, J=5.5 Hz, 2H), 3.77 (s, 3H), 2.03 (s, 3H), 1.76–1.64 (m, 1H), 1.62–1.52 (m, 1H), 1.44–1.35 (m, 1H), 1.01 (d, J=6.5 Hz, 3H), 0.87 (d, J=6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.0, 171.4, 169.9, 158.4, 149.2, 142.6, 111.0, 107.0, 52.6, 52.3, 43.5, 41.9, 25.1, 23.3, 23.2, 21.8; IR (neat): 3447–3166, 1741, 1700, 1651, 1608 cm^{-1}; FABHRMS calcd for $C_{16}H_{24}N_3O_4$ (M+H): 322.1767, found: 322.1768.

3.2.19. (2*R*,*S*)-[4-(2-Acetylamino-4-methyl-pentanoyl)-pyridin-2-ylamino]-acetic acid methyl ester (33*rac*). β-Strand mimetic **33** (5 mg, 16 μmol) was dissolved in THF (2 mL) and 1,8-diazabicyclo[5.4.0]undec-7-ene (25 μL, 167 μmol) was added. The reaction was subjected to microwave irradiation, 80 °C for 0.5 h. The reaction was concentrated under reduced pressure and the residue was filtered through a short path of silica gel with EtOAc as eluent to give **33***rac* (4 mg, 80%) as determined by chiral HPLC; $[\alpha]_D^{20}$ 0 (*c* 0.25, $CHCl_3$); ^{1}H NMR identical as for β-strand mimetic **33**.

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Supplementary data

^{1}H NMR and ^{13}C NMR spectra for all new isolated compounds as well as chiral chromatograms of compounds **33** and **33***rac* are included. This material is available free of charge via the Internet at http://www.sciencedirect.com. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.08.080.

References and notes

1. Nesloney, C. L.; Kelly, J. W. *Bioorg. Med. Chem.* **1996**, *4*, 739–766.
2. Loughlin, W. A.; Tyndall, J. D. A.; Glenn, M. P.; Fairlie, D. P. *Chem. Rev.* **2004**, *104*, 6085–6117.
3. Sauer, F. G.; Pinkner, J. S.; Waksman, G.; Hultgren, S. J. *Cell* **2002**, *111*, 543–551.
4. Sauer, F. G.; Remaut, H.; Hultgren, S. J.; Waksman, G. *Biochim. Biophys. Acta* **2004**, *1694*, 259–267.
5. Larsson, A.; Johansson, S. M. C.; Pinkner, J. S.; Hultgren, S. J.; Almqvist, F.; Kihlberg, J.; Linusson, A. *J. Med. Chem.* **2005**, *48*, 935–945.
6. Larsson, A.; Spjut, S.; Kihlberg, J.; Almqvist, F. *Synthesis* **2005**, 2590–2596.
7. Svensson, A.; Larsson, A.; Emtenas, H.; Hedenstrom, M.; Fex, T.; Hultgren, S. J.; Pinkner, J. S.; Almqvist, F.; Kihlberg, J. *ChemBioChem* **2001**, *2*, 915–918.
8. Kjellén, P.; Brunsberg, U.; Broddefalk, J.; Hansen, B.; Vestberg, M.; Ivarsson, I.; Engström, Å.; Svejgaard, A.; Kihlberg, J.; Fugger, L.; Holmdahl, R. *Eur. J. Immunol.* **1998**, *28*, 755–767.
9. Dzhambazov, B.; Nandakumar, K. S.; Kihlberg, J.; Fugger, L.; Holmdahl, R.; Vestberg, M. *J. Immunol.* **2006**, *176*, 1525–1533.
10. Holm, L.; Kjellen, P.; Holmdahl, R.; Kihlberg, J. *Bioorg. Med. Chem.* **2005**, *13*, 473–482.
11. Holm, L.; Bockermann, R.; Wellner, E.; Bäcklund, J.; Holmdahl, R.; Kihlberg, J. *Bioorg. Med. Chem.* **2006**, *14*, 5921–5932.
12. Hagihara, M.; Anthony, N. J.; Stout, T. J.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 6568–6570.
13. Phillips, S. T.; Piersanti, G.; Ruth, M.; Gubernator, N.; van Lengerich, B.; Bartlett, P. A. *Org. Lett.* **2004**, *6*, 4483–4485.
14. Phillips, S. T.; Rezac, M.; Abel, U.; Kossenjans, M.; Bartlett, P. A. *J. Am. Chem. Soc.* **2002**, *124*, 58–66.
15. Smith, A. B.; Charnley, A. K.; Mesaros, E. F.; Kikuchi, O.; Wang, W. Y.; Benowitz, A.; Chu, C. L.; Feng, J. J.; Chen, K. H.; Lin, A.; Cheng, F. C.; Taylor, L.; Hirschmann, R. *Org. Lett.* **2005**, *7*, 399–402.
16. Smith, A. B.; Guzman, M. C.; Sprengeler, P. A.; Keenan, T. P.; Holcomb, R. C.; Wood, J. L.; Carroll, P. J.; Hirschmann, R. *J. Am. Chem. Soc.* **1994**, *116*, 9947–9962.
17. Smith, A. B.; Keenan, T. P.; Holcomb, R. C.; Sprengeler, P. A.; Guzman, M. C.; Wood, J. L.; Carroll, P. J.; Hirschmann, R. *J. Am. Chem. Soc.* **1992**, *114*, 10672–10674.
18. Smith, A. B.; Benowitz, A. B.; Guzman, M. C.; Sprengeler, P. A.; Hirschmann, R.; Schweiger, E. J.; Bolin, D. R.; Nagy, Z.; Campbell, R. M.; Cox, D. C.; Olson, G. L. *J. Am. Chem. Soc.* **1998**, *120*, 12704–12705.
19. Saitton, S.; Del Tredici, A. L.; Mohell, N.; Vollinga, R. C.; Boström, D.; Kihlberg, J.; Luthman, K. *J. Med. Chem.* **2004**, *47*, 6595–6602.
20. Saitton, S.; Kihlberg, J.; Luthman, K. *Tetrahedron* **2004**, *60*, 6113–6120.
21. Rocca, P.; Cochennec, C.; Marsais, F.; Thomas-dit-Dumont, L.; Mallet, M.; Godard, A.; Queguiner, G. *J. Org. Chem.* **1993**, *58*, 7832–7838.
22. Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed* **2003**, *42*, 4302–4320.
23. Wen, J. J.; Crews, C. M. *Tetrahedron: Asymmetry* **1998**, *9*, 1855–1858.
24. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156.
25. Lubell, W. D.; Rapoport, H. *J. Am. Chem. Soc.* **1987**, *109*, 236–239.
26. Myers, A. G.; Zhong, B. Y.; Movassaghi, M.; Kung, D. W.; Lanman, B. A.; Kwon, S. *Tetrahedron Lett.* **2000**, *41*, 1359–1362.
27. Pietraszkiewicz, M.; Jurczak, J. *Tetrahedron* **1984**, *40*, 2967–2970.
28. Estel, L.; Marsais, F.; Queguiner, G. *J. Org. Chem.* **1988**, *53*, 2740–2744.
29. Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849–3862.
30. Prepared from *tert*-butyl acrylate, which was cleaved to the corresponding aldehyde with ozone. Solid phase bound triphenyl phosphine was used to prevent over oxidation of the aldehyde.
31. Michel, P.; Ley, S. V. *Synthesis* **2003**, 1598–1602.
32. Marshall, G. R. *Tetrahedron* **1993**, *49*, 3547–3558.
33. Pitts, W. J.; Wityak, J.; Smallheer, J. M.; Tobin, A. E.; Jetter, J. W.; Buynitsky, J. S.; Harlow, P. P.; Solomon, K. A.; Corjay, M. H.; Mousa, S. A.; Wexler, R. R.; Jadhav, P. K. *J. Med. Chem.* **2000**, *43*, 27–40.
34. Marshall, J. A.; Garofalo, A. W. *J. Org. Chem.* **1993**, *58*, 3675–3680.