Stereoselective synthesis of a β -methylthio α -amino α -lactam dipeptide, a S-methyl-Cys-Val mimic

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Abstract

Pursuing β -substituted α -N-(Fmoc)amino- γ -lactam (Agl) dipeptides by displacements of the alcohol corresponding β -hydroxy- α -amino- γ -lactam (Hgl) residue, nucleophilic ring opening of cyclic sulfamidate **3** with thiocyanate has provided entry to trans- β -methylthio-Agl derivative **5** for use as a constrained S-methyl Cys derivative.

Introduction

Peptides are typically flexible and may adopt multiple conformers in solution. Among methods to restrict peptide movement and improve receptor binding affinity, cyclization has proven successful since the team at Merck led by Drs. Freidinger and Veber introduced α -amino- γ -lactam (Agl) residues into LH-RH.[1] Since their pioneering research, many have used Agl residues to favor peptide turn conformations by constraining ω , ϕ and ψ backbone dihedral angles.[2] Adding β -substituents to Agl residues has since been perceived as a means to enhance mimicry potential by simultaneously constraining backbone and side (χ) dihedral angles.[3-5]

Recently, a set of β -substituted α -amino- γ -lactam residues were synthesized using β -hydroxy- α -amino- γ -lactam (Hgl) residue **1** as a convenient precursor (Figure 1).[5,6] Mitsunobu reactions on the trans isomer of Hgl trans-**1** with pro-nucleophiles having pKa values between 3 and 7 provided a variety of cis- β -substituted Agl analogs **2a-g** in 49-80% yields.[6] Moreover, treatment of trans-Hgl **1** with diphenylphosphoryl azide (DPPA) as a hydrazoic acid equivalent under Mitsunobu conditions gave in 60% yield the corresponding β -azido-Agl residue, which was further converted to its phenyltriazole counterpart in 80% yield by copper-catalyzed azide alkyne cycloadditions.[6]

Attempts to employ Mitsunobu reaction on cis-Hgl cis-**1** gave however only dehydro-lactam. Cyclic sulfamidate **3** was thus synthesized from cis-Hgl cis-**1** to disfavor β -elimination to dehydro-lactam.[6] Ring opening of sulfamidate **3** has already provided β -azido-Agl **4a** and constrained protected cysteine **4b** (Figure 1). Exploring the chemistry of sulfamidate **3** further, we now report a method to provide constrained S-alkyl Cys residues (e.g., **5**).

Figure 1: Synthesis of 4-substituted Agl residues by way of the Mitsunobu reaction and cyclic sulfamidate ring opening.

Results and Discussion

β -Thiocyano-Agl **4c** was synthesized by reacting sulfamidate **3** with potassium thiocyanate in 1:1 DMF/DCM in 92% yield. Reduction of thiocyanide **4c** with NaBH₄ and alkylation with iodomethane by way of a constrained Cys thiolate intermediate provided thioether **5** in 65% yield from **4c** (Scheme 2).[7]

Scheme 2: Synthesis of constrained S-methyl Cys derivative [5]

Conclusions

Methylthio-Agl 5 may be considered a constrained isoleucine analog. Moreover, S-alkylation with other electrophiles may further expand the diversity of trans- β -substituted Agl residues. The synthesis of such amino acid residues with constrained backbone and side chain geometry, and their subsequent insertion into peptides is now under investigation and will be reported in due time.

Experimental

tert-Butyl (3S, 4S, 2'R)-2-[3-(Fmoc)amino-4-thiocyanato-2-oxopyrrolidin-1-yl]-3-methylbutanoate

A solution of sulfamidate 3 (1 eq., prepared according to ref 6) in a mixture of DCM (2 mL) and DMF (2 mL) was treated with potassium thiocyanate (3 eq.), stirred at 45 °C for 16 h, poured into 1 M NaH₂PO₄, and extracted with DCM. The combined organic phase was washed with brine, dried, filtered, evaporated to a residue, that was purified by column chromatography using a step gradient of 10-30% EtOAc in hexane. Evaporation of the collected fractions gave thiocyanide 4c as a white solid (): R_f = 0.3 (30% EtOAc in hexane); mp 56-60 °C; $[\alpha]_D^{25}$ 24° (c 1, CHCl₃); FT-IR (neat) ν_{max} 3321, 2973, 2155, 1707, 1523, 1449, 1391, 1370, 1239, 1150, 1106, 1043, 781, 759, 738 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.76 (d, J = 7.6 Hz, 2H), 7.59 (ddd, J = 7.4, 3.8, 0.6 Hz, 2H), 7.41 (t, J = 7.4 Hz, 2H), 7.32 (td, J = 7.5, 1.0 Hz, 2H), 5.48 (s, 1H), 4.46 (m, 3H), 4.31 (s, 2H), 4.23 (t, J = 6.8 Hz, 1H), 3.83 (dd, J = 18.1, 9.1 Hz, 1H), 3.49 (t, J = 9.4 Hz, 1H), 2.23 (m, 1H), 1.48 (s, 9H), 1.02 (d, J = 6.7 Hz, 3H), 0.97 (d, J = 6.8 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 169.0, 156.5, 143.5, 141.3, 127.8, 127.1, 125.1, 120.1, 109.7, 82.7, 67.6, 60.9, 57.1, 48.1, 47.0, 45.9, 29.0, 28.0, 22.0, 19.5, 19.3; HRMS (ESI-TOF) m/z [M+Na]⁺ calcd for C₂₉H₃₃N₃O₅S 558.2033 found, 558.2017.

tert-Butyl (3S, 4S, 2'R)-2-[3-(Fmoc)amino-4-methylthio-2-oxopyrrolidin-1-yl]-3-methylbutanoate

A solution of thiocyanide 4c (1 eq.,) in EtOH (95%, 1 mL) was added drop-wise to a stirred solution of NaBH₄ (5 eq.,) in EtOH (95%, 1 mL) at rt. The mixture was stirred for 2 h, treated with iodomethane (2 eq.,), stirred for 1 h, and treated with a solution of 1N HCl (2 mL). The mixture was extracted with EtOAc (3×5 mL). The combined organic phase was washed with brine, dried, filtered, evaporated to a residue, that was purified by column chromatography using a step gradient of 10-30% EtOAc in hexane. Evaporation of the collected fractions gave thioether 5 as a light yellow oil (): R_f = 0.5 (30% EtOAc in hexane); $[\alpha]_D^{25}$ 45° (c 0.2, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.76 (d, J = 7.5 Hz, 2H), 7.60 (d, J = 7.4 Hz, 2H), 7.39 (t, J = 7.5 Hz, 2H), 7.31 (td, J = 7.5, 1.0 Hz, 2H), 5.26 (s, 1H), 4.45 (d, J = 9.1 Hz, 1H), 4.43 (d, J = 7.0 Hz, 2H), 4.34 (t, J = 8.9 Hz, 1H), 4.24 (t, J = 7.0 Hz, 1H), 4.06 (dd, J = 9.4, 7.5 Hz, 1H), 3.32 – 3.24 (m, 1H), 3.21 (t, J = 9.2 Hz, 1H), 2.24 – 2.14 (m, 4H), 1.47 (s, 9H), 1.00 (d, J = 6.7 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 171.1, 169.5, 156.4, 143.8, 141.3, 127.7, 127.1, 125.2, 120.0, 82.3, 67.3, 60.7, 57.6, 47.8, 47.1, 45.7, 28.8, 28.1, 22.0, 19.4, 13.6; HRMS (ESI-TOF) m/z [M+Na]⁺ calcd for C₂₉H₃₆N₂O₅S 547.2237 found, 547.2228.

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