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Parallel synthesis of 19-membered ring macro-heterocycles via intramolecular thioether formation

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ABSTRACT

Starting from resin-bound orthogonally protected lysine, the generation of 19-membered ring macro-heterocycles via intramolecular thioether formation is described. The on resin cyclization occurred by the coupling of *p*-fluoro-*m*-nitro benzoic acid or bromo acetic acid followed by intramolecular substitution S_NAr or S_N2 displacement of the fluoro and bromo groups, respectively. The described approaches present versatile synthetic routes toward the synthesis of libraries of macro-heterocycles in an attempt to establish lead drug candidates. The desired cyclic products were obtained in good yields and good purities.

Macrocycles are known for their broad range of activities including antitumor and antibiotic activities, such as those of the structurally complex vancomycin family.[1] Reported approaches on the solid-phase synthesis of macrocyclic compounds include intramolecular nucleophilic substitution, intramolecular amide formation, disulfide formation, and intramolecular Suzuki reactions.[2,3] In this Letter, we describe an efficient method for the synthesis of 19-membered macrocycles on the solid-support based on an intramolecular **S_NAr** or **S_N2** nucleophilic substitution. Thioether cyclic peptidomimetics are often used as mimics of the disulfide cyclic peptides.[4] The replacement of the disulfide bond with a more stable thioether bond increases the metabolic stability of peptides.[4] Cyclic-thioether peptides have always been of special interest and the synthesis of analogs of bioactive compounds incorporating lanthionine, a monosulfide analog of cysteine and a key constituent of peptide antibiotics, continues to receive considerable attention.[4–7]

Cyclic-thioether peptides are reported to display a wide variety of activities, including anti-cardiolipin antibodies[5,6] and vascular cell adhesion molecule-1 (VCAM-VLA-4) antagonists.[7] Thioether formation is also used as a technique for the generation of cyclopeptidomimetic libraries.[6,8,9] Known natural products which contain a cyclic thioether include the lantibiotics, a class of polycyclic peptides antibiotics containing intrachain sulfide bridges. To this class of natural products belong nisin, a preservative in the food industry, and epidermin, a therapeutic agent against acne.[4]

Starting from resin-bound orthogonally protected Fmoc-Lys-(Boc) **1**, thioether macrocyclic compounds **6** were synthesized following stepwise Fmoc deprotection and standard repetitive Fmoc-amino-acid couplings yielding the linear tripeptide **2** (Scheme 1).[10] Following removal of the Fmoc group, the resulting free amine was acylated with bromo acetic acid to form compound **3**. The Boc group on the side chain of lysine was deprotected and the generated amine was coupled to Fmoc-Cys(Trt)-OH in the presence of HBTU. The cysteine side chain was deprotected in the presence of TFA. The resin was treated with a solution of DIEA in DCM to undergo an S_N2 intramolecular cyclization yielding the corresponding resin-bound thioether cyclic peptide **5**. Following Fmoc deprotection and acylation with a variety of carboxylic acids in the presence of DIC and HOBt, the resin was cleaved and the desired products were obtained in good yields and good purity (Table 1).

Similarly, we applied S_NAr reactions for the generation of 19-membered cyclic peptides. Previous reports on the solid-phase S_NAr macrocyclization using 2-fluoro-5-nitrobenzoic acid described the formation of 13- to 16-membered ring systems as β-turn peptidomimetics.[11] Thioaryl macrocyclic peptides active at melanocortin receptors have been reported[12] and potent selective hMCR5 receptor antagonists have been identified.[12] The solid-phase S_NAr has been also applied as a versatile synthetic route for the cyclization of tripeptides on solid-support.[12]

As outlined in Scheme 2, starting from the same resin **1**, thioaryl macrocyclic compounds **11** were synthesized following stepwise Fmoc deprotection and standard repetitive Fmoc-amino-acid couplings, yielding the linear peptide **7**, following removal of the Fmoc group. The resulting free amine **7** was acylated with 4-fluoro-3-nitrobenzoic acid to form compound **8**. The Boc group on the side chain of lysine was deprotected and the generated free amine was coupled to Fmoc-Cys(Trt)-OH in the presence of HBTU. The Trt group was removed and the resin was washed and allowed to react in DCM in the presence of DIEA to generate, following intramolecular S_NAr cyclization, the corresponding resin-bound thioaryl cyclic

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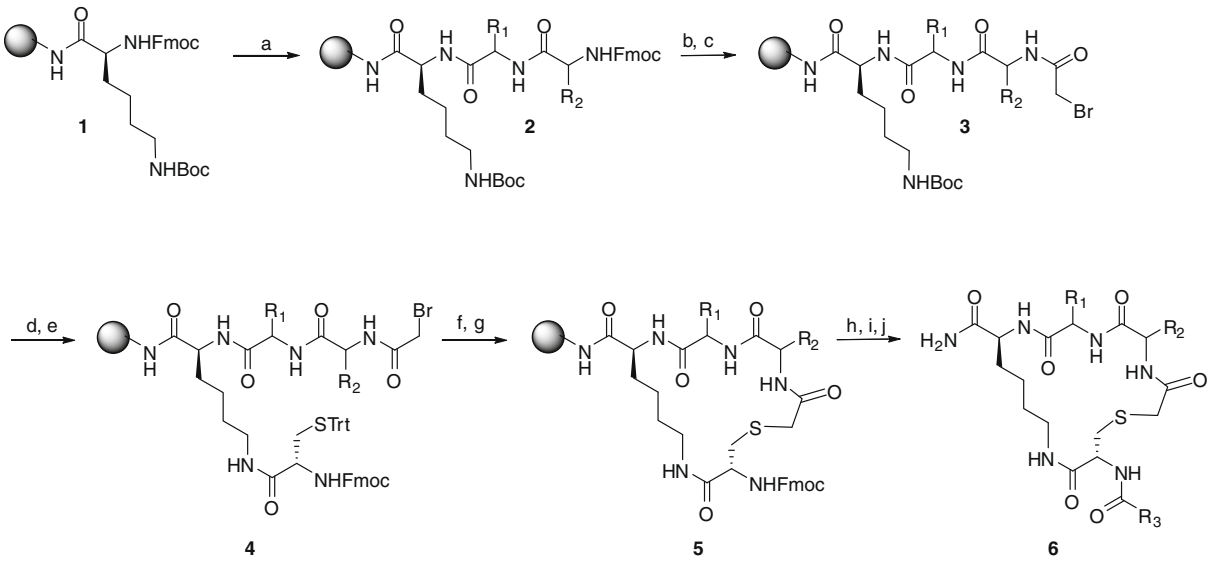
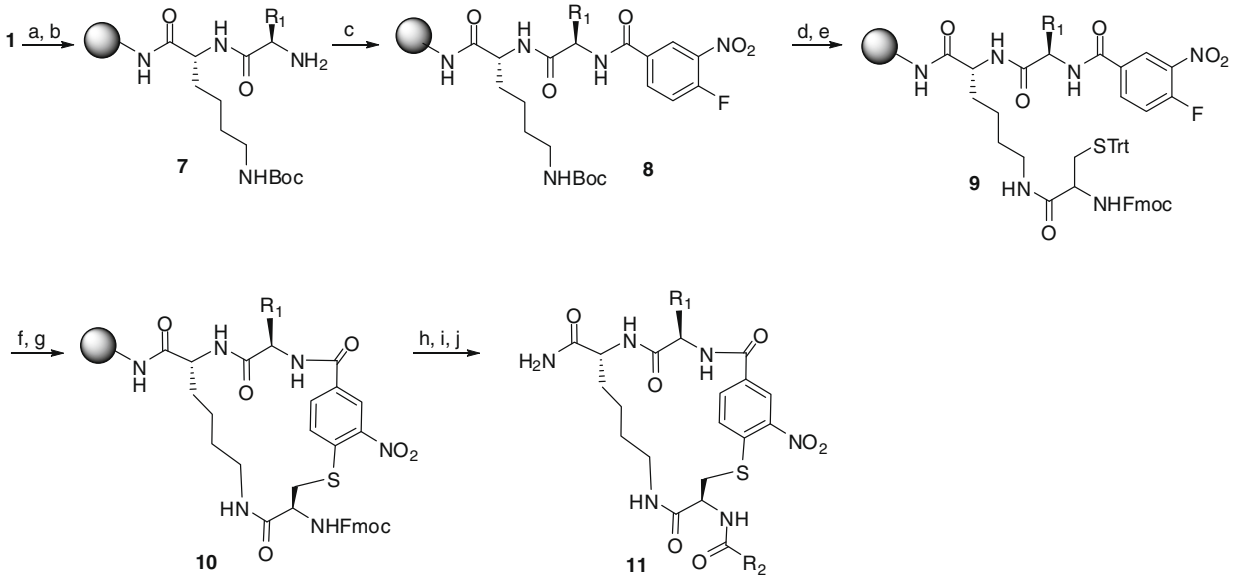


Scheme 1. Reagents and conditions: (a) Fmoc SPPS; (b) 20% piperidine in DMF; (c) bromoacetic acid, DIC; (d) 55% TFA in DCM; (e) Fmoc-Cys(Trt)-OH, HBTU, DMF; (f) TFA/$(Bu^t)_3SiH$/DCM (5:5:90); (g) DIEA in DCM overnight; (h) 20% piperidine in DMF; (i) R_3COOH, DIC, HOBt; (j) HF/anisole (90 min).

Table 1

Entry	R_1	R_2	R_3	Expected MW	Observed $[M+H]^+$	Purity[a] (%)
6a	$-CH(CH_3)_2$	$-CH_2C_6H_5$	$-CH_2C_6H_5$	652.8	653.4	80
6b	$-CH(CH_3)_2$	$-CH_2C_6H_5$[b]	$-CH_2C_6H_5$	652.8	653.4	80
6c	$-CH(CH_3)_2$	$-CH_3$	$-CH_2C_6H_5$	576.2	577.3	65
6d	$-CH(CH_3)_2$	$-CH_2C_6H_5$	$-C_6H_4(C_6H_5)$	714.3	715.3	80
6e	$-CH(CH_3)_2$	$-CH_3$	$-C_6H_4(C_6H_5)$	638.2	639.5	65
6f	$-CH(CH_3)_2$	$-CH_2C_6H_5$	H	534.2	535.3	70

[a] The products were run on a Vydac column, gradients 5–95% solvent B (0.1% TFA in ACN) in 7 min. The purity was estimated on analytical traces at λ = 214 nm and 254 nm.
[b] D-Phenylalanine was used for the diversity R_2.



Scheme 2. Reagents and conditions: (a) Fmoc SPPS; (b) 20% piperidine in DMF; (c) 4-fluoro-3-nitro-benzoic acid, DIC; (d) 55% TFA in DCM; (e) Fmoc-Cys(Trt)-OH, HBTU, DMF; (f) TFA/$(Bu^t)_3SiH$/DCM (5:5:90); (g) DIEA in DCM overnight; (h) 20% piperidine in DMF; (i) R_3COOH, DIC, HOBt; (j) HF/anisole (90 min).

peptide. The Fmoc group was deprotected and the generated amine was treated with different carboxylic acids in the presence of DIC and HOBt to yield, following cleavage of the resin, the corresponding 19-membered thioaryl cyclic peptides (Table 2).

We have presented a straightforward approach for the parallel synthesis[8] of macrocyclic compounds by intramolecular S_NAr or S_N2 nucleophilic substitution. The approach can be used for the high-throughput synthesis of macro-heterocycles.

Table 2

Entry	R_1	R_2	Predicted MW	Observed $[M+H]^+$	Purity[a] (%)
11a	$-CH_2C_6H_5$	$-CH_2$-adamantane	718.8	719.2	73
11b	$-CH_2C_6H_5$	$-CH_2-(4\text{-methoxy})C_6H_4$	690.7	691.1	70
11c	$-CH_2C_6H_5$	$-CH_2-(3\text{-fluoro})C_6H_4$	678.7	679.1	75
11d	$-CH_2C_6H_5$	$-(CH_2)_3-C_6H_5$	688.7	689.2	72
11e	$-CH_3$	$-CH_2$-adamantane	642.7	643.2	76
11f	$-CH_3$	$-CH_2-(4\text{-methoxy})C_6H_4$	614.6	615.1	70
11g	$-CH_3$	$-CH_2-(3\text{-fluoro})C_6H_4$	602.6	603.1	72
11h	$-CH_3$	$-(CH_2)_3-C_6H_5$	612.7	613.1	73
11i	$-CH(CH_3)_2$	$-CH_2$-adamantane	670.8	671.2	74
11j	$-CH(CH_3)_2$	$-CH_2-(4\text{-methoxy})C_6H_4$	642.7	643.1	68
11k	$-CH(CH_3)_2$	$-CH_2-(3\text{-fluoro})C_6H_4$	630.6	631.1	72
11l	$-CH(CH_3)_2$	$-(CH_2)_3-C_6H_5$	640.7	641.2	73
11m	$-(CH_2)_3-$[b]	$-CH_2$-adamantane	668.8	669.2	75
11n	$-(CH_2)_3-$[b]	$-CH_2-(4\text{-methoxy})C_6H_4$	640.7	641.2	66
11o	$-(CH_2)_3-$[b]	$-CH_2-(3\text{-fluoro})C_6H_4$	628.6	629.1	66
11p	$-(CH_2)_3-$[b]	$-(CH_2)_3-C_6H_5$	638.7	639.1	68

[a] The products were run on a Vydac column, gradients 5 to 95% solvent B (0.1% TFA in ACN) in 7 min. The purity was estimated on analytical traces at $\lambda = 214$ nm and 254 nm.

[b] Derived from proline.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.05.029.

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