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Solid phase synthesis of constrained 13-membered peptide macrocycles employing Fukuyama–Mitsunobu alkylations

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ABSTRACT

Efficient strategies for the solid phase synthesis of constrained macrocyclic peptides are valuable tools for the generation of potentially biologically active compound libraries. In particular, the use of covalent linkers as hydrogen bond surrogates for the initiation and stabilization of α-helical secondary structures, resulting in the formation of a 13-membered macrocycle, is a validated approach. For these purposes, a straightforward synthetic pathway was developed, employing natural amino acids bearing usual protecting groups and mediated through two Fukuyama–Mitsunobu alkylation reactions on unprotected 1,3-propanediol on solid phase. The linear precursors were obtained in good purity and moderate yields, and the final cyclization step was carried out in solution.

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Introduction

Macrocyclic peptides have been the subject of intense research due to their often enhanced affinity, biodisponibility and stability properties compared to their linear precursors.[1–3] In particular, when constrained in defined secondary structures, they constitute useful tools as biological probes and lead to therapeutics, targeting in particular protein–protein interactions.[4,5] Replacement of the hydrogen bond existing between residues *i* and *i*+4 of an α-helix by covalent bonds leads to the formation of 13-membered peptidic macrocycles. Such entities were shown to be able to propagate further structuration towards the extended C-terminal end. This strategy was initiated by Cabezas and Satterthwait[6] and extensively developed by Arora and co-workers,[7,8] as demonstrated by the synthesis of a variety of α-helical peptides displaying improved biological properties.[9–11] Efficient solid phase strategies have been developed for the production of these macrocyclic peptides.[12–15] Alewood and co-workers employed a solution phase strategy relying on a reductive amination reaction to produce 13-membered macrocyclic peptides of structure **A** (Fig. 1).[16]

Herein, with the objective to facilitate the production of libraries, a solid phase method for the synthesis of 13-membered macrocyclic peptides of structure **6** (Scheme 1) has been developed. They may serve as α-helix inducers when extended at the C-terminal extremity, or as simple turn mimetics. Ultimately, the introduction of adequate side chains should produce potentially biologically active compounds.

The Fukuyama–Mitsunobu alkylation is a mild and very efficient procedure for the synthesis of secondary amines.[17] It has been successfully employed on solid phase for the N-alkylation of amino acids, including backbone *N*-Et scan of Leu-enkephalin,[18] synthesis of *N*-alkylated cyclic tripeptides,[19] N-allylation reactions assisted by microwaves,[20] and N-alkylation of an ornithine side chain.[21] The preparation of 13-membered amine bridged macrocyclic enkephalin analogues using *N*-protected ethanolamine has also been reported.[22] We envisioned a resin-supported synthetic strategy towards macrocyclic peptides of structure **6** (Scheme 1), relying on successive Fukuyama–Mitsunobu alkylations, in which 1,3-propanediol would serve as the covalent linker, and employing only α-amino acids. To exemplify our strategy, only amino acids non-functionalized on their side chains were chosen.

Results

Our synthesis started with the reaction of a resin-bound *o*-nitrobenzenesufonyl (*o*-Ns) protected amino acid with excess unprotected 1,3-propanediol, DIAD (diisopropyl azodicarboxylate) and PPh_3 under controlled microwave irradiation (50 °C, 15 min) or at room temperature (14 h) in anhydrous THF. DIAD was used because it was shown to be superior to DEAD (diethyl azodicarboxylate) on solid phase.[22] The desired *N*-alkylated amino acid **1** was obtained exclusively, as determined by HPLC and mass spectrometry analysis after cleavage of the resin with TFA.[23]

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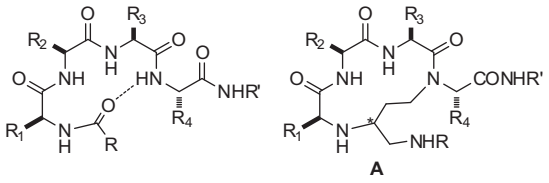
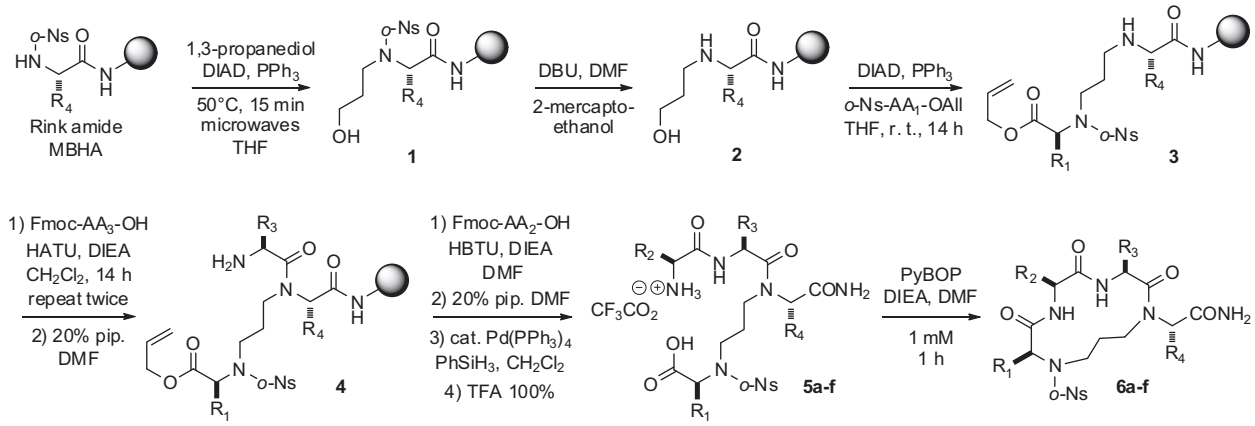


Figure 1. Hydrogen bond pattern of an α-helical turn between residues *i* and *i*+4 (left), and previously synthesized covalent mimetics **A** (right).[16]

Satisfyingly, intermolecular double alkylation was not observed, confirming that the separation of functional groups attached on solid phase (pseudo-dilution) was successfully exploited. Literature data indicate that, in solution phase, as expected, an additional hydroxyl protecting group was required for the synthesis of polyamines with symmetrical diols.[24] After *o*-Ns deprotection under standard conditions,[25,26] a second Fukuyama–Mitsunobu alkylation on **2** with excess *o*-Ns/allyl protected amino acid allowed the construction of the diaminopropane motif **3**. We are aware of only one example of this type of 'reverse' setup in which the alcohol is bound to the resin and the acidic functional group in excess is in solution,[27] although a few intramolecular examples have been reported.[28] Because usual side reactions such as dehydration and substitution by deprotonated DIAD happen on the alcohol partner,[28] we were pleased to see that the reaction proceeded well. Indeed, cleavage from the resin and HPLC analysis indicated in all cases that the expected product was predominantly or exclusively obtained.

Chain extension to give the *N*-alkylated peptide of structure **4** is known to be a difficult coupling reaction, highly dependent on the steric bulk of the amino acid side chains.[20] The use of the HATU/DIEA system with 5 equiv of Fmoc protected amino acids in CH_2Cl_2 as a solvent gave satisfactory results, leading to full conversion after two 14 h coupling cycles for **4a–d**. However, approximately 30% remaining starting material were observed after three repeated cycles for **4e** and **4f**. Following further chain extension with Fmoc protected amino acids under standard conditions and removal of the Fmoc and allyl groups, the peptides were cleaved from the resin with neat TFA to obtain the linear precursors **5a–f**. Addition of water as a scavenger in the cleavage mixture was deleterious, resulting in the formation of some C-terminal acid contaminating the amide, in agreement with recent literature data.[29] Considering the very low yields described in the literature after a second alkylation step on solid-phase for the synthesis of polyamines,[27] the high purity of the crude mixtures and the moderate yields obtained after HPLC purification seemed satisfactory (Table 1).

The cyclization of resin-bound **5** was attempted with different solvents (DMF, CH_2Cl_2 and THF) and coupling agents (PyBOP, HATU and DIC). However, as evidenced by HPLC and MALDI mass spectroscopy analysis, only traces of products were obtained, along with dimer and trimer cyclic compounds and other unidentified side products. Fortunately, in solution, the cyclization step proceeded cleanly and in less than one hour with PyBOP/DIEA in DMF to give the desired products **6a–f**. This system gave slightly cleaner HPLC profiles than HATU/DIEA and shorter reaction times



Scheme 1. Synthetic pathway to 13-membered macrocyclic peptides.

Table 1
Outcome of the synthesis of **6a–f**

Sequences	**5**	**6**		
	% yields[a]	% from 10 mM of **5**[b]	% from 1 mM of **5**[b]	% yields from 1 mM of **5**[c]
GAGA* **a**	41 (57:43)	79 (21)	95 (5)	52 (>99:1)
GALA* **b**	31 (61:39)	26 (56)	69 (27)	42 (br)
GFLA* **c**	46 (70:30)	45 (53)	74 (19)	41 (br)
LALA* **d**	24 (57:43)	n.d.	75 (25)	35 (92:8)
LFAL* **e**	24 (61:39)	75 (24)	95 (<5)	53 (95:5)
LAAF* **f**	15 (51:49)	84 (8)	86 (<5)	31 (71:29)

X* denotes the *N*-propyl amino acid X (AA_4).

[a] Isolated yields after cleavage from the resin and HPLC purification. The ratios between rotamers are given in parenthesis, as measured by ^{1}H NMR integration in d_6-DMSO at 298 K.

[b] The % macrocyclic products **6** formed are given as measured by HPLC at 220 nm at the indicated linear precursor **5** concentrations in DMF (% dimer are given in parenthesis; the remaining to 100% corresponds to unidentified products integrated at 220 nm).

[c] Isolated yields from 1 mM reactions of **5** after HPLC purification. The ratios of rotamers are given in parenthesis, as measured by ^{1}H NMR integration in d_6-DMSO at 298 K. br: broad signals observed in the ^{1}H NMR spectra due to conformational exchange.

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