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A new strategy for total solid-phase synthesis of polymyxins

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ABSTRACT

Polymyxin B and E are used as a 'last line' therapy for infections caused by serious Gram-negative bacteria due to their highly efficient antibacterial activity and nephrotoxicity. Many research groups have been performed on designing polymyxin analogues by chemical synthesis in order to decrease the nephrotoxicity and increase the antibacterial activity simultaneously. In this study, we developed a new strategy for total solid phase synthesis of polymyxins and their analogues. This method is achieved by anchoring the amine side chain of Dab9 on resin first and on-resin cyclization at last. Comparing to the mostly used chemical synthetic method for polymyxins which involves solid phase peptide synthesis followed by liquid phase cyclization, the method reported here is more convenient and efficient. Therefore, this new strategy may be a good replacement for current chemical synthetic method in designing polymyxin analogues.

Polymyxins B (PMB) and E (colistin) are polycationic lipodecapeptides which were first isolated from *Bacillus polymyxa* more than 60 years ago.[1] The only difference of PMB and colistin is the *D*-form amino acid in position 6 which is *D*-Phe in PMB and *D*-Leu in colistin (Fig. 1). With the increase in the multidrug-resistant infection caused by Gram-negative bacterium, polymyxins show efficient antibacterial activity toward untreatable serious infection cases.[2] However, in recent years, polymyxins are reported to have nephrotoxicity in clinical studies.[3] Therefore, this main concern limits the wide application of polymyxins in medical treatment and turns polymyxins into a 'last line' therapy for Gram-negative pathogen infections.[4] In order to decrease toxicity and improve antibacterial activity, many research groups have taken efforts to discover polymyxin analogs by changing N-terminal fatty acyl chain,[5] the number of *L*-α,γ-diaminobutyric acid (Dab) residues,[6] and the amino acid residue at the position 6 or 7 in the cyclic ring.[7] Most recently, Magee and his co-workers reported a new kind of polymyxin analog by replacing Dab at position 3 with *L*-2,3-diaminopropanoic acid residue (Dap) and substituting N-terminal fatty acyl chain with biaryl amides.[8] In addition, Li group also reported a modification strategy for polymyxin via replacing position 6 or 7 residue with long aliphatic chain.[9] Both these two methods achieved polymyxin analogues with improved in vitro antibacterial activity and decreased renal cytotoxicity.

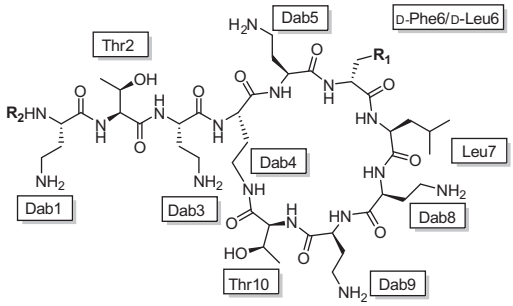

Figure 1. Structures of polymyxin B2, E2, and polymyxin analog Dap3 5f: R_1 = phenyl (B2), R_1 = isopropyl (E2), R_2 = 6-methylheptanoyl (B2 and E2), R_2 = 4-Biphenylcarboxylic acid (Dap-3 5f[8]).

The chemical synthetic method which Magee or Li utilized was divided into two steps: firstly, a partially protected linear peptide was obtained through solid phase peptide synthesis (SPPS) before cleavage from resin; secondly, cyclization step was carried out in liquid phase followed by global deprotection to achieve final polymyxin analog. However, this two-steps synthesis strategy limits the overall efficiency. In the process of studying the structure–activity relationships (SAR) of polymyxin, we found that

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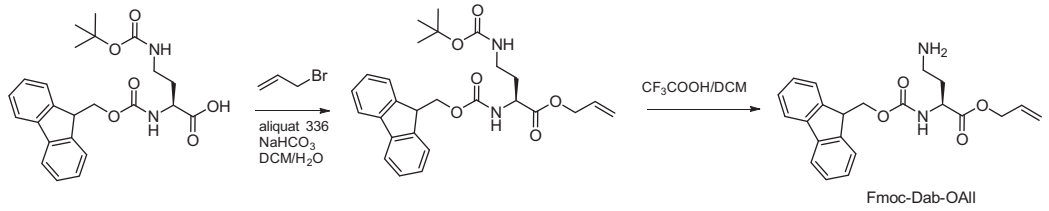

Scheme 1. Synthesis of building block Fmoc-Dab-OAll.

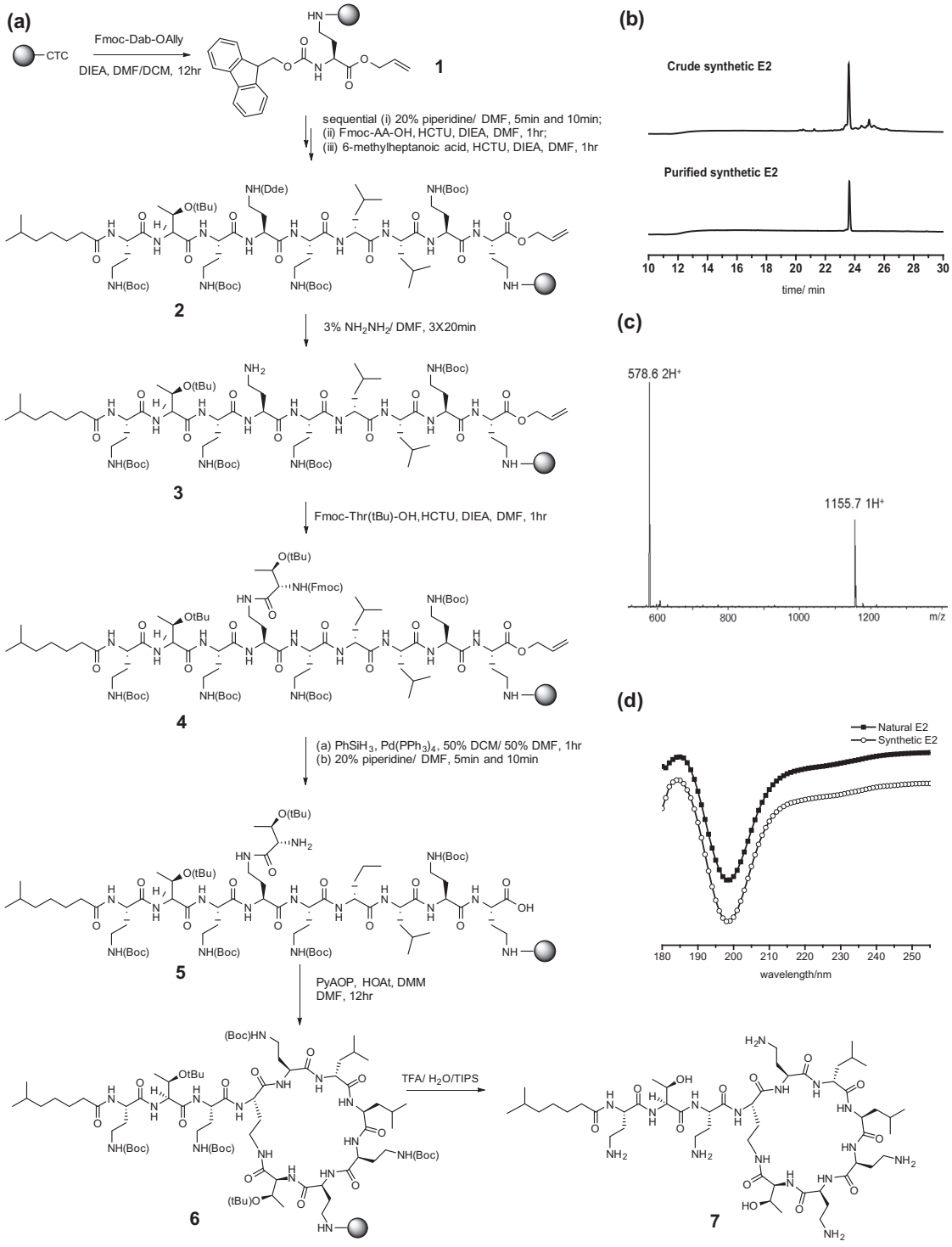

Figure 2. (a) Solid phase total synthesis of polymyxin E2; (b) RP-HPLC traces of crude E2 (above) and purified synthetic E2 (below); (c) ESI-MS spectrum of purified synthetic E2; (d) CD spectra of natural E2 (above) and synthetic E2 (below).