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Solid phase total synthesis of callipeltin E isolated from marine sponge *Latrunculia* sp.

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ABSTRACT

Solid phase total synthesis of callipeltin E (**1**), truncated linear peptide isolated from marine sponge, *Latrunculia* sp. was achieved. Our strategy based on traditional Fmoc-SPPS was in common use TFA-treatment final deprotection to reach callipeltin E (**1**) contained acid-sensitive βMeOTyr.

Callipeltin E (**1**) is an acyclic hexapeptide isolated from the marine sponge *Latrunculia* sp. by D'Auria and co-workers in 2002.[1] Callipeltin E (**1**) was shown to be a truncated, open-chain derivative of callipeltin A (**2**) (Fig. 1). Callipeltin A (**2**), isolated from the shallow water sponge *Callipelta*,[2,3] is the first natural peptide found to act against HIV and shows antifungal activity and potent cytotoxicity against several human carcinoma cell lines.[4,5,6] Callipeltin E (**1**) is composed of unique amino acids: *N*-methylalanine (MeAla), β-methoxytyrosine (βMeOTyr), *N*-methylglutamine (MeGln), leucine (Leu), D-arginine (D-Arg), and D-allothreonine (D-alloThr). The configuration of βMeOTyr, which could not be determined in Minale's isolation study,[3] was determined as 2*R*,3*R* by D'Auria and co-workers[7] using chemical degradation of callipeltin A (**2**) and derivatization of the resulting amino acids, and also by Konno et al.[8] using NMR comparison of four diastereoisomeric tripeptides, independently. On the other hand, by employing quantum mechanical calculation of coupling constants, it was suggested by Bifulco and co-workers[9] that both of the threonine residues in callipeltin A (**2**) have a D-allo configuration. Based on these reports, callipeltin E (**1**) was determined to have the structure H-D-alloThr-D-Arg-Leu-*N*-MeGln-(2*R*,3*R*)-βMeOTyr-*N*-MeAla-OH. Lipton reported the solid phase synthesis and confirmation of the configurational assignment of callipeltin E (**1**).[10] Although Lipton did not use acidic conditions in the study due to the acid-sensitive nature of the βMeOTyr residue, we recently reported that

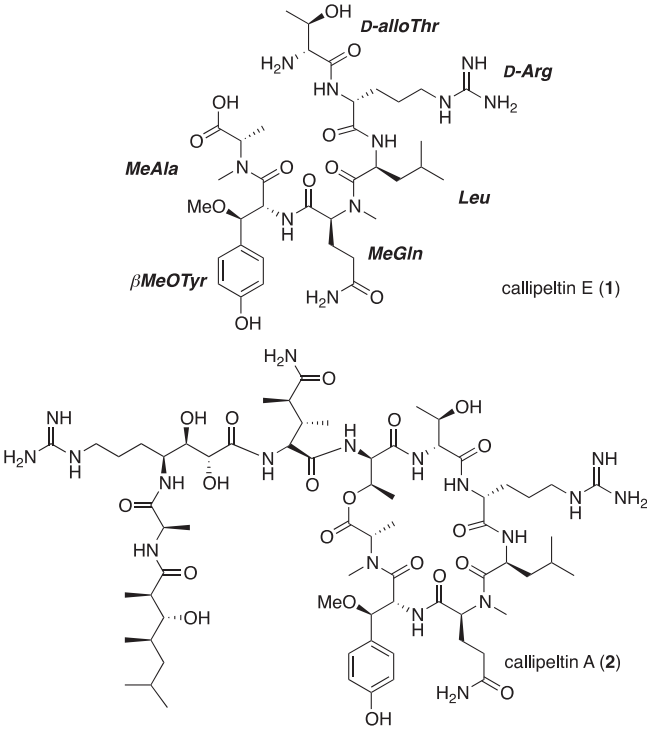

Figure 1. Callipeltin E (**1**) and callieplin A (**2**).

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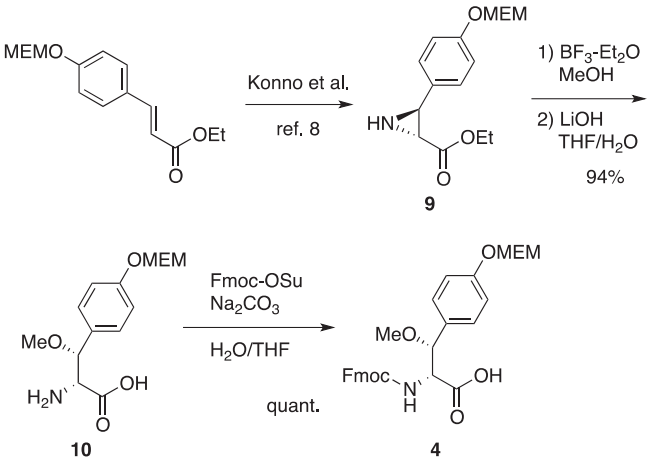
βMeOTyr was not decomposed by TFA treatment.[8] The results were a major advantage to construct the depsipeptide such as callipeltins and similar complex molecules in the point of permission to employ the traditional Fmoc-solid phase peptide synthesis (Fmoc-SPPS).

For the solid phase total synthesis of callipeltin A (**2**) and its analogues using the traditional Fmoc-SPPS strategy, we decided to synthesize callipeltin E (**1**) as a model peptide. Herein, we report the efficient solid phase synthesis of callipeltin E (**1**) based on the Fmoc-SPPS strategy.

Our approach to the synthesis of callipeltin E (**1**) employed traditional Fmoc-SPPS, that is, both Fmoc deprotection using piperidine and TFA-mediated final deprotection. Prior to the total synthesis of callipeltin E (**1**), the necessary four unusual amino acids with protecting groups, Fmoc-MeAla-OH (**3**), Fmoc-βMeOTyr(OMEM)-OH (**4**), Fmoc-MeGln-OH (**5**), and Fmoc-D-allo-oThr-OH (**8**) were synthesized (Scheme 1).

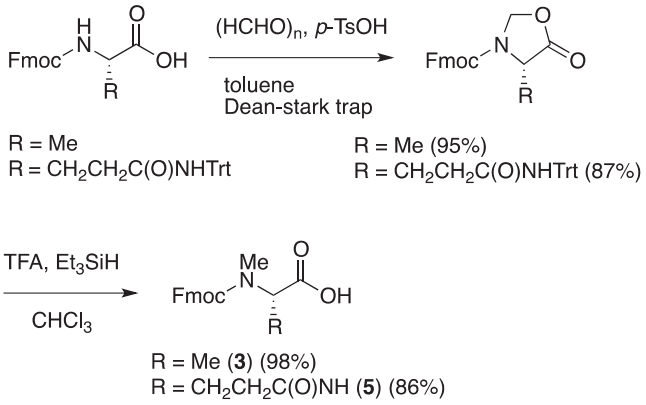
The required residue Fmoc-(2*R*,3*R*)-βMeOTyr(OMEM)-OH (**4**) was synthesized from the previously reported aziridine derivative (**9**) in three steps with 94% overall yield[8,11] (Scheme 2). In the previous report,[8] aziridine was opened using catalytic $BF_3{\cdot}Et_2O$ and 10 equiv of MeOH in CH_2Cl_2, but the diastereoselectivity of the ring opening was moderate (3:1). In an attempt to improve diastereoselectivity, we found that treatment of aziridine (**9**) with a catalytic amount of $BF_3{\cdot}Et_2O$ in MeOH at room temperature gave anti-methoxyamine, and then an ethoxycarbonyl group was saponified to afford the amino acid (**10**). It was noted that MeOH for methoxy source was effective to use as a solvent. Under these conditions, anti-substitution was observed, leading to no loss of diastereoselectivity (>20:1). The amino acid (**10**) was protected with Fmoc-OSu to yield Fmoc-(2*R*,3*R*)-βMeOTyr(OMEM)-OH (**4**) in quantitative yield.



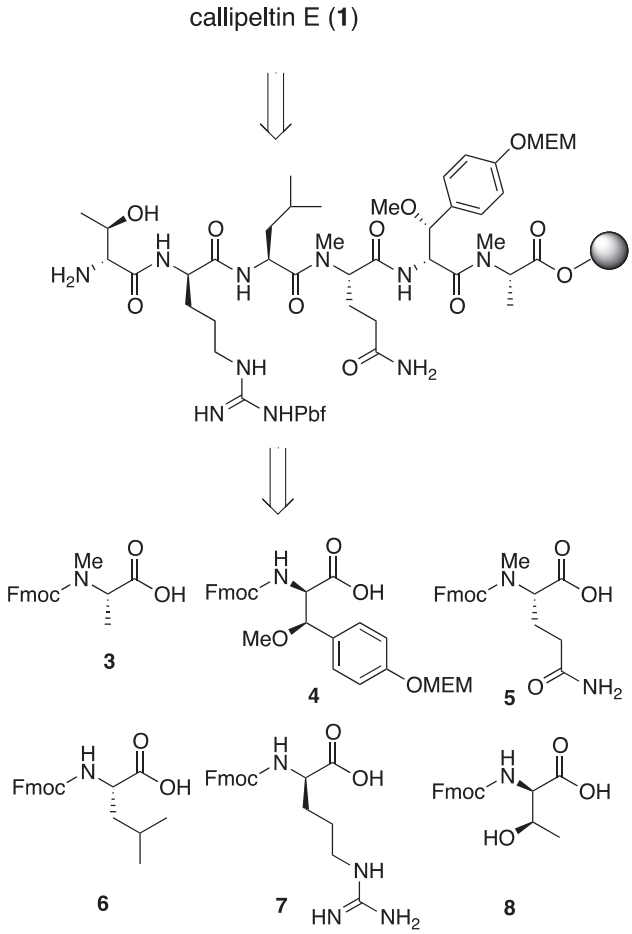
Scheme 2. Preparation of Fmoc-(2*R*,3*R*)-βMeOTyr(OMEM)-OH (**4**).

Fmoc-N^{α}-MeAla-OH (**3**) and Fmoc-N^{α}-MeGln-OH (**5**) were prepared from commercially available Fmoc-N^{α}-Ala-OH and N^{δ}-trityl-N^{α}-Fmoc-Gln-OH via the oxazolidinone intermediates employing Freidinger's procedure[12] in 93% and 75% overall yields, respectively (Scheme 3).

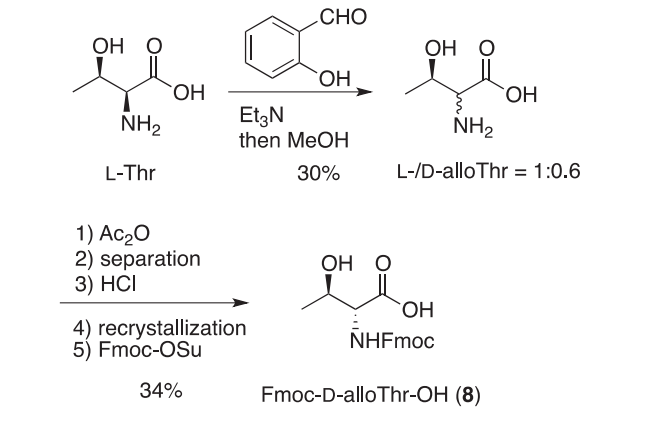
Fmoc-D-alloThr-OH (**8**) was prepared from L-Thr in the study reported by Yajima et al.[13] L-Thr was subjected to epimerization using salicylaldehyde to give a diastereomeric mixture of L-Thr



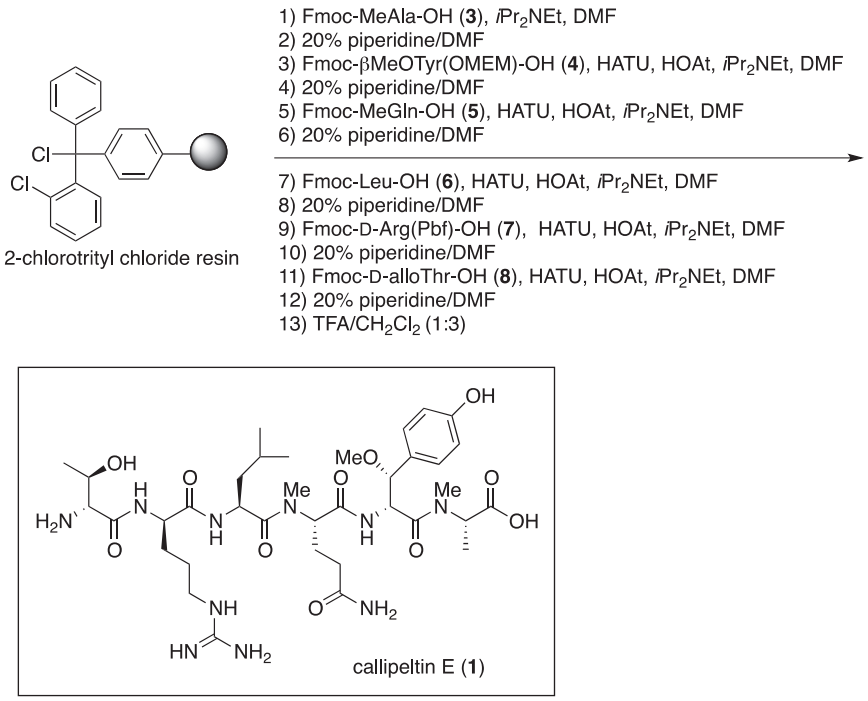
Scheme 3. Preparation of Fmoc-*N*-MeAla-OH (3) and Fmoc-*N*-MeGln-OH (**5**).



Scheme 1. Synthetic plan for callipeltin E (**1**).



Scheme 4. Preparation of Fmoc-D-alloThr-OH (**8**).



Scheme 5. Solid phase synthesis of callipeltin E (**1**).

and D-alloThr in a molar ratio of 1:0.6. After acetylation of the amino group followed by converting the ammonium salt, separation of Ac-D-alloThr-OH ammonium salt as a soluble in EtOH and Ac-L-Thr-OH ammonium salt as a less-soluble diastereomeric salt by filtration obtained Ac-D-alloThr-OH as 50% de. The sequence of hydrolysis, recrystallization and Fmoc protection gave pure Fmoc-D-alloThr-OH (**8**) in 9% overall yield (Scheme 4).

Callipeltin E (**1**) was synthesized by Fmoc-based SPPS according to the route shown in Scheme 5. As a solid support, 2-chlorotrityl chloride resin was selected. Fmoc-*N*-MeAla-OH (**3**) was reacted with 2-chlorotrityl chloride resin in DMF in the presence of *i*Pr_2NEt. The Fmoc group of the resulting resin was removed with 20% piperidine/DMF and Fmoc-(2*R*,3*R*)-βMeOTyr(OMEM)-OH (**4**) was condensed by HATU[14]/HOAt[15] in the presence of *i*Pr_2NEt. The same deprotection/condensation procedure was repeated for the introduction of Fmoc-*N*-MeGln-OH (**5**), Fmoc-Leu-OH (**6**), Fmoc-D-Arg(Pbf)-OH (**7**), and Fmoc-D-alloThr-OH (**8**). In the attempt at several coupling reagents, all coupling conditions monitored by Keiser test[16] were optimized to use the HATU/HOAt combination. Finally, the resin was treated with TFA/CH_2Cl_2 (1:3 v/v) to cleave from the resin and deprotection to give crude callipeltin E (**1**). The crude product showed a single major peak on HPLC and was purified by preparative RP-HPLC to afford callipeltin E (**1**) in 0.93% overall yield. Although decomposed products were not shown on the HPLC profile under these conditions, treatment of resin with TFA in a mixture of H_2O as an additive afforded by-products with desmethoxy or desmethyl functional groups of the βMeOTyr residue. The spectroscopic data (^{1}H NMR, ESIMS) on synthetic **1** were identical to those of synthetic callipeltin E reported by Lipton et al.[10] or isolated natural product callipeltin E[1] within normal error limits.

In conclusion, we achieved the solid phase total synthesis of callipeltin E (**1**) based on the traditional Fmoc-SPPS. The configuration of callipeltin E (**1**) was identified using Lipton's revised structure. This procedure is easily applicable to solid phase synthesis of the analogues of callipeltins using commercially available Fmoc-amino acids. The total synthesis of callipeltin A (**2**) is now underway.

Acknowledgements

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