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Graphical Abstract

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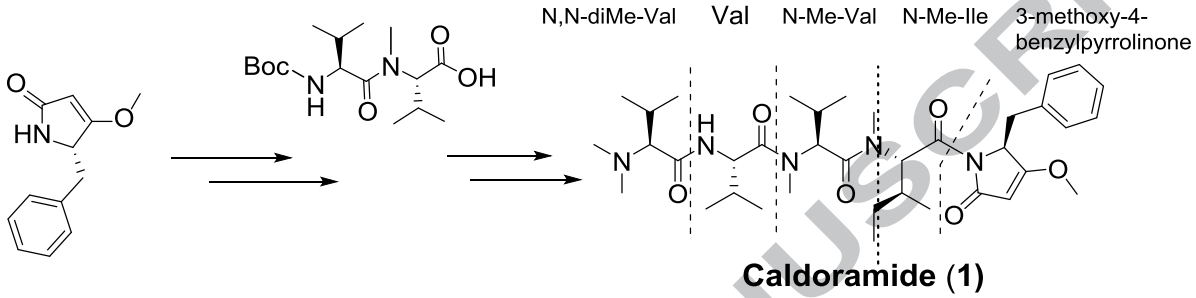

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Total synthesis of modified pentapeptide, Caldoramide

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ABSTRACT

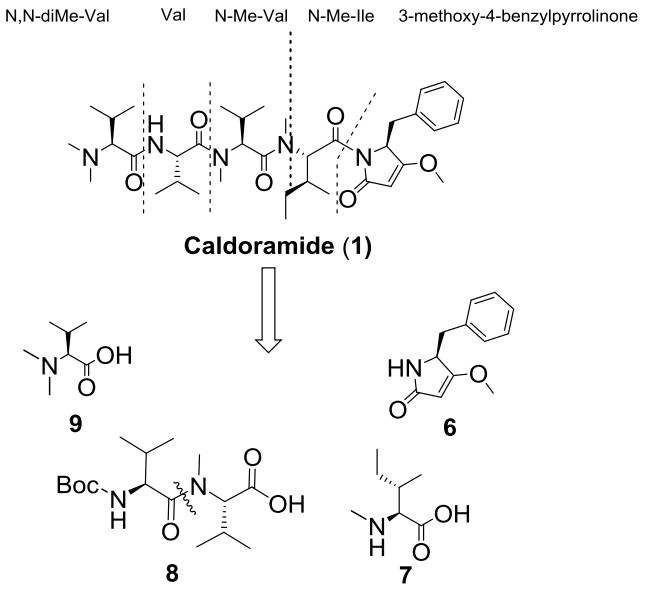
Total synthesis of modified pentapeptide, caldoramide, a cytotoxic linear pentapeptide from the marine cyanobacterium *Caldora penicillate* is described. Notable features of the route include the efficient preparation of three key fragments and final assembly to the natural product *via* sequential amide couplings. The spectral data of the synthetic compound was found to be in comparison with that of the isolated natural product.

Introduction

Peptides are important bioactive natural products which are present in many marine species and these have been a subject of extensive research.[1] Both linear and cyclic peptides have always attracted great attention for their unique structures and potent pharmacological activities.[2] In addition, peptides have also played an important role as therapeutic agents and key mediators of biological function due to their low toxicity and high specificity. Caldoramide (**1**) is a marine derived linear pentapeptide natural product, isolated from cyanobacterium *Caldora penicillata* by Luesch and coworkers in 2016.[3] Structurally it comprises of a peptidic backbone bearing a dimethylated *N*-terminal amino acid and *C*-terminal benzyl pyrrolinone moiety. It has structural similarities to belamide A (**2**),[4] dolastatin 15 (**3**),[5,6] dolastatin 10 (**4**),[7,8] and simplostatin (**5**)[9] (Fig 1) which are potential anti-cancer agents, advanced to clinical trials. Caldoramide has shown moderate cytotoxicity similar to that of belamide.[10] In particular, dolastatins 10 (**4**) and 15 (**3**) have exhibited extraordinary cytotoxicity to cancer cells.[11,12] Their interesting biological activities have aroused synthetic efforts which resulted in several drug leads that have advanced to clinical trials.[13]

In continuation of our interest in the total synthesis of biologically active natural products, the similarity in structure of caldoramide with the potential anti-cancer agents prompted us to undertake the total synthesis of caldoramide (**1**). Recently Wunder A. et al have reported the first total synthesis of caldoramide,[14] but the optical rotation was not found to be in comparison with that of the isolated natural product and some other deviations were observed in the spectral data. We herein report an efficient total synthesis of caldoramide (**1**), a new closely related structural analogue of belamide A and dolastatin 15.

Results and discussion



Scheme 1. Retrosynthetic strategy of Caldoramide (**1**)

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Retrosynthetic analysis (scheme 1) of caldoramide revealed the presence of a linear peptide chain linked to 3-methoxy-4-benzylpyrrolinone ring at the C-terminus similar to that of belamide A and *N*,*N*-dimethyvaline at the *N*-terminus of the peptide chain. Linked to the pyrrolinone ring was found a linear chain of amino acids containing *N*-Me-isoleusine residue, *N*-Me-valine and valine which was finally linked to the *N*-terminal, *N*,*N*-dimethyvaline residue. We envisaged that caldoramide (**1**) could be assembled in a rapid and convergent manner by the sequential coupling of the pyrrolidone **6**, with the above mentioned amino acid residues.

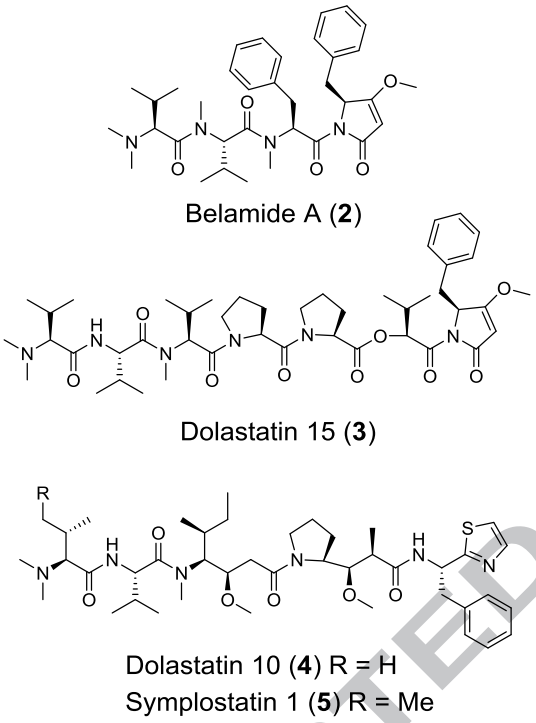
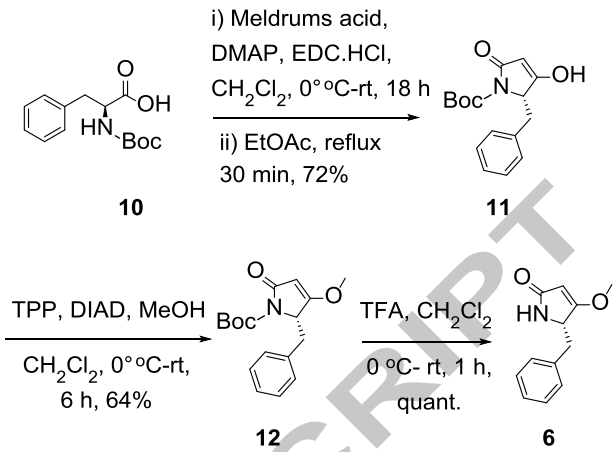


Fig 1. Stucturally related natural products

Preparation of known C-terminal pyrrolinone moiety (**6**)[4,15] commenced with Boc-L-phenyl alanine **(10) as the starting material** (**Scheme 2**) which was condensed with Meldrum's acid using *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDC) and 4-(dimethylamino) pyridine (DMAP). Subsequent reflux in ethyl acetate facilitated the anticipated thermal cyclization to the desired pyrrolinone (**11)** in 72% yield Alkylation of the enol functionality under Mitsunobu conditions with diisopropyl azodicarboxylate (DIAD), triphenylphosphine (TPP) and methanol selectively generated the desired 4-methoxypyrrolinone (**12**) in 64% yield. Final deprotection of Boc group with trifluoro acetic acid (TFA) in dichloromethane produced **6 in quantitative yield**. Spectral data confirmed the formation of the desired compound as reported.

Having successfully prepared the pyrrolidinone moiety (**6**) our attention turned towards the synthesis of the peptide fragments **8** and **9** (scheme 1). The known peptide fragment **8** was prepared following the reported procedures. The spectral data of the prepared compound was correlated with the reported values,[4] and found to be in complete agreement.

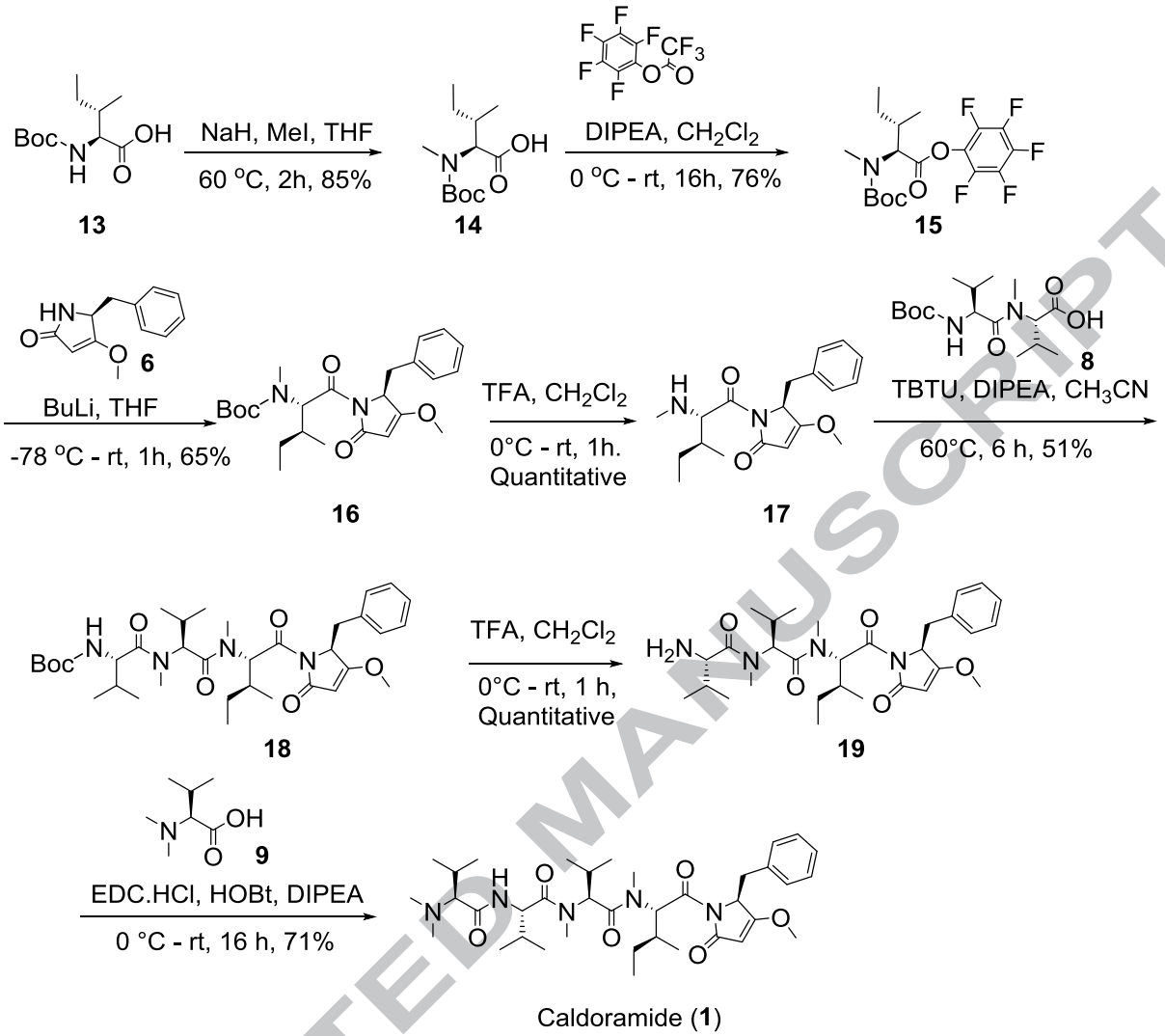


Scheme 2. Synthesis of 3-methoxy-4-benzyl pyrrolinone

After having successfully synthesized peptide **8** we prepared the *N*,*N*-dimethylvaline **9** residue present at the *N*-terminus as reported in the literature.[16]

With the fragments **6**, **8** and **9** now in our hand, the construction of the linear pentapeptide, caldoramide was achieved sequentially from the C-terminus to the *N*-terminus as depicted in the scheme 3.

Commercially available *N*-Boc isoleucine (**13**) was taken as the starting material and treated with sodium hydride and methyl iodide in THF to give the corresponding *N*-methylated acid derivative (**14**) in 85 % yield. Then compound **14** was converted to the pentafluorophenyl ester **15** (76 % yield) by treatment with perflourophenyl-2,2,2 triflouroacetate in the presence of DIPEA in methylene chloride. The activated ester **15** was reacted with the anion of **6** generated by treatment with BuLi in THF at -78 ^{o}C which gave compound **16** in 65% yield. Subsequent removal of Boc group by treatment of **16** with TFA in methylene chloride gave compound **17** in quantitative yield. Amide coupling of fragment **17** with the previously prepared peptide **8** was carried out using 2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) in acetonitrile in the presence of DIPEA which gave compound **18** in 51 % yield. Removal of the Boc group with TFA in methylene chloride gave compound **19** in quantitative yield. Completion of the synthesis then required a coupling with compound **9** prepared earlier. Then as a final step, compound **19** was coupled with the acid **9** using EDC.HCl in presence of HOBT and DIPEA in DMF to produce caldoramide in 71 % yield. Gratifyingly, the physical and the spectroscopic data obtained for the synthetic caldoramide **1** (^{1}H and ^{13}C NMR) and the measured specific rotation, $[\alpha]^{25}_{D}$ +8.4 (*c* 0.36, MeOH) cf. + 11.1 were in good agreement with that provided for the isolated natural product,[3] providing convincing evidence that the absolute configuration of **1** is identical to those reported by Luesch and co-workers (see the supporting information).



Scheme 3: Synthetic Scheme for the preparation of Caldoramide

In summary, we have completed the total synthesis of the cyano bacterium-derived linear pentapeptide natural product, caldoramide. It is anticipated that the synthetic route described can be useful to prepare related class of compounds. This convergent synthesis outlines the preparation of the key fragments, an efficient and rapid coupling to yield the natural product.

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Supplemantary data

Supplementary data includes experimental procedures and spectroscopic data of all new compounds.

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Highlights:

- Total synthesis of a modified pentapeptide, Caldoramide.
- The total synthesis involved a convergent approach
- Sequential amide couplings were adapted to prepare the natural product.
- The spectral data was in good agreement with the reported values.