Tetrahedron Letters 57 (2016) 3837–3840

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

An improved route for the synthesis of Rolloamide B

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ARTICLE INFO

Article history:
Received 5 May 2016
Revised 17 June 2016
Accepted 12 July 2016
Available online 15 July 2016

Keywords:
Rolloamide B
IBCF
Total synthesis
Natural product
Macrocycles

ABSTRACT

A high yielding method for the synthesis of the cyclic heptapeptide Rolloamide B has been described. An effective isobutyl chloroformate (IBCF) mediated direct coupling reaction was introduced to improve the synthetic route towards Rolloamide B. Furthermore, preliminary bioassays indicated potential activity against Gram-negative bacteria and fungi.

Introduction

At the present time, modern medicine tends to develop novel compounds that are biologically more active than those found in nature. However, natural products are themselves very important since they are the actual models for some synthetic drugs. Peptides have drawn considerable attention as therapeutic agents due to their role as key mediators of biological function together with their low toxicity and high specificity.[1,2] Various cyclic peptides, such as caspofungin, vancomycin, gramicidin S, bacitracin, polymyxin B, colistin and valinomycin, are powerful antimicrobial agents[3–5] (Fig. 1). In contrast to linear peptides, cyclic peptides are more stable against proteolytic degradation due to the absence of free N- or C-terminus as well as reduced conformational freedom.[6]

Antimicrobial peptides (AMPs) are potent, broad spectrum, antibiotics which demonstrate potential as novel therapeutic agents. Rolloamide B is a cyclic heptapeptide consisting of serine, isoleucine, proline, phenylalanine, leucine, proline and isoleucine (Fig. 2). It was first isolated from the marine sponge *Eurpon. laughlini* in 1997,[7] however, it was not possible to solve the structure of the peptide at the time of isolation since only a small amount of the compound was available. A re-isolation of Rolloamide B in 2002 once again yielded only trace amounts but allowed structure elucidation.[7] In 2013, Katritzky and co-workers reported the first total synthesis of Rolloamide B.[8] Nevertheless, the route had some drawbacks including; (i) several reaction steps (16 step), (ii) long reaction times and (iii) low overall yield (3.6%).[8]

The aim of the present work was to improve the efficiency of the chemical synthesis by reducing the number of the steps. This is desirable so as to avoid a lengthy separation process, extensive purification of the intermediate compounds and to save time and resources while increasing chemical yield.

In the present study, we have developed an improved synthesis in 11 steps with an overall yield of 27%. Additionally, we screened the antimicrobial activity of the natural product, which was found to possess activity against several Gram-negative bacteria as well as antifungal activity.

Results and discussion

In previous work, the amino acid coupling was achieved over 2 steps involving benzotriazole activation followed by amino acid coupling.[8] Herein, we used isobutyl chloroformate (IBCF) as a

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http://dx.doi.org/10.1016/j.tetlet.2016.07.044
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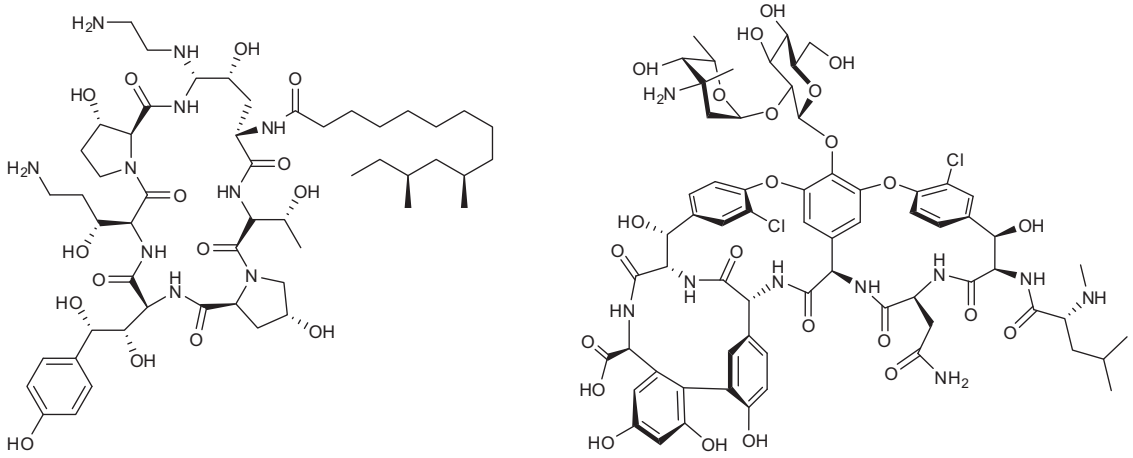


Figure 1. Caspofungin (antifungal) and vancomycin (antibacterial).

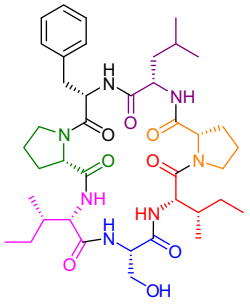


Figure 2. Rolloamide B.

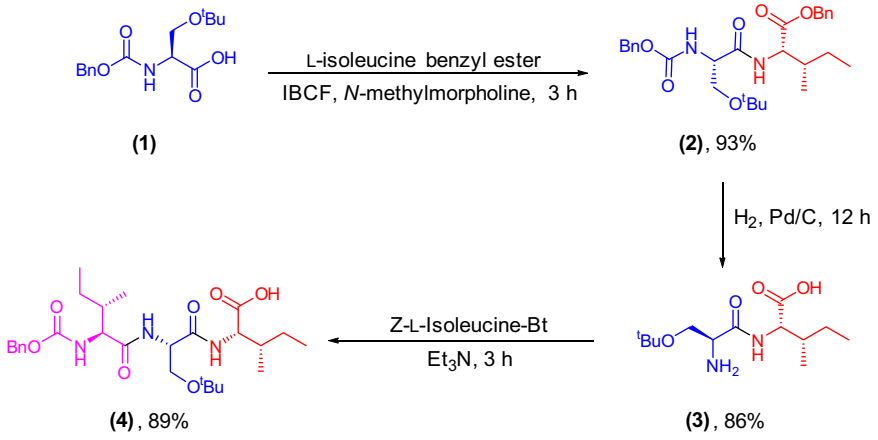
direct coupling agent with minimal side-reactions and simple workup.[9] This method provided good yields with minimal racemization.

Firstly, we prepared intermediate **4** by the linear coupling of amino acid residues using IBCF and *N*-methylmorpholine as base. Compound **1** was coupled with L-isoleucine benzyl ester to give **2** in 93% yield followed by deprotection of the Cbz-group with hydrogen and catalytic Pd/C, affording **3** in 86% yield. Coupling of **3** with Z-L-isoleucine-Bt provided tripeptide **4** in 89% yield (Scheme 1).

Next, we prepared tetrapeptide **11** by the same coupling procedure that was used in the preparation of tripeptide **4**. Coupling **5** with proline benzyl ester followed by Boc-deprotection using a HCl-dioxane solution, gave dipeptide **7** in 97% yield. The dipeptide **9** was obtained in 88% yield by coupling Boc-L-proline benzotriazole **8** with L-leucine. Coupling of dipeptides **7** and **9** using IBCF gave **10** in 90% yield. Deprotection of the Boc-group gave tetrapeptide **11** in 96% yield (Scheme 2).

Finally, we prepared the linear heptapeptide **13** in 83% yield from the coupling of tripeptide **4** and tetrapeptide **11**, followed by deprotection of the Cbz group with hydrogen and catalytic Pd/C. Cyclization of linear heptapeptide **13** by pentafluorophenyl diphenylphosphinate (FDPP) mediated peptide coupling followed by *tert*-butyl deprotection using trifluoroacetic acid gave Rolloamide B **14** in 80% yield (Scheme 3).

Rolloamide B was then screened against 4 bacterial strains (Gram-negative *Klebsiella pneumoniae*, *Proteus vulgaris*, and *Pseudomonas aeruginosa*, Gram-positive *S. aureus*). Although it exhibited low activity against Gram-positive *Staphylococcus aureus*,



Scheme 1. Synthesis of *Z*-L-Ile-L-Ser-(*t*Bu)-L-Ile-OH (tripeptide intermediate **4**).