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A facile and efficient method for synthesis of macrocyclic lipoglycopeptide

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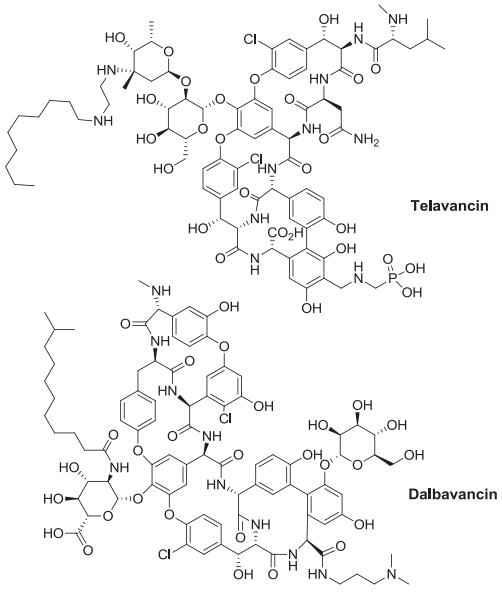
ABSTRACT

An efficient and practical method for macrocyclic lipoglycopeptide synthesis was developed and utilized to synthesize lipoglycosylated derivatives of Tyrocidine A. The method is based on solid-phase peptide synthesis using 2-chlorotrityl resin as the solid-phase support and lipoglycosyl amino acids as building blocks. This synthetic method should be generally applicable to various macrocyclic lipoglycopeptides.

1. Introduction

Lipoglycopeptide antibiotics are actinomycete-derived antibiotics with unique tricyclic or tetracyclic heptapeptide cores that are usually glycosylated and sometimes have additional lipophilic fatty acid side,[1] such as telavancin[2] and dalbavancin[3] (Fig. 1). The glycopeptides antibiotics are the most important drugs in current use for the treatment of Gram-positive bacterial infections.[4] Dalbavancin and telavancin contain a heptapeptide core, common to all glycopeptides, which enables them to inhibit transglycosylation and transpeptidation (cell wall synthesis), and their lipophilic side chains can prolong their half-life, help to anchor the agents to the cell membrane and increase their activity against Gram-positive cocci. In addition to inhibiting cell wall synthesis, telavancin and oritavancin are also able to disrupt bacterial membrane integrity and increase membrane permeability, oritavancin also inhibits RNA synthesis.[2,5] However, Lipoglycopeptides can only be acquired through extraction of natural products,[6] biotransformation,[7] and semisynthesis,[8] which limit the application of lipoglycopeptides in clinic.

Recently, great efforts have been made to obtain macrocyclic peptides and their mimics.[9] In 2009, our group has successfully realized the first total synthesis of macrocyclic glycopeptides and this method has been applied to prepare other macrocyclic glycopeptides.[10] However, chemical synthesis of macrocyclic lipoglycopeptide was not reported and attracted our attention.



Figiure 1. Chemical structure of telavancin and dalbavancin.

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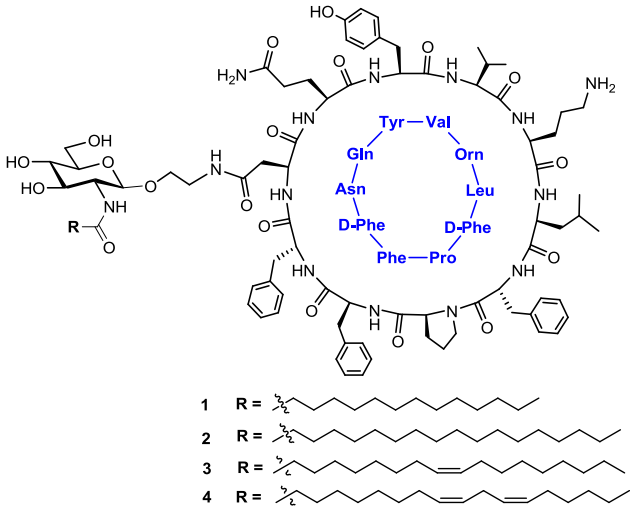
Tyrocidine A is a cyclic decapeptide isolated from *Bacillus* bacteria that exhibits strong bactericidal activities and it has been suggested to primarily target the bacterial membrane. In spite of its severe side effects, Tyrocidine A represents an attractive lead compound for the development of new antibacterial drugs.[11] Herein, a facile and efficient method of synthesizing macrocyclic lipoglycopeptide is described and four lipoglycosyl Tyrocidine A derivatives were designed and synthesized. Further biological evaluation was in progress (Fig. 2).



Figiure 2. Chemical structure of Tyrocidine A lipoglycosylated derivatives.

2. Results and discussion

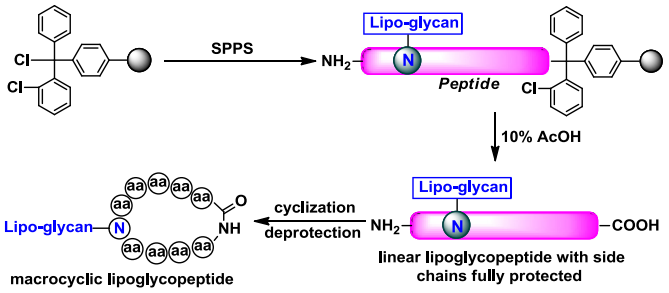
2.1. Synthetic design

Our plan was to first construct lipoglycosylated liner decapeptides by solid-phase peptide synthesis (SPPS) and then unite their C-terminus and N-terminus via solution phase with good yield to obtain macrocyclic lipoglycopeptides. It has been reported that glycosylated amino acids could be directly used as building blocks, just as other simple amino acids in the SPPS.[12] Therefore, in our research, the lipoglycosylated amino acids were directly coupled to the peptide backbone for solid-phase lipoglycosylated liner peptides assembly.

In addition, as the free amino and/or carboxylic groups within their amino acid side chains contained in the title compounds, it was necessary to fully protect the active group within the side chains during the cyclization reaction, which ensured the efficiency of the coupling reactions between the peptide C- and N-termini.[13] In this regard, the extremely acid-sensitive 2-chlorotrityl resin can be an applicable SPPS support, as peptides can be released from this resin using 10% acetic acid, which does not affect the protecting groups of amino acid side chains. Another advantage of using fully protected glycopeptides for cyclic glycopeptide synthesis is that these substrates would be easily soluble in organic solvents, which should be particularly helpful for the cyclization reaction. On the basis of the above considerations, we envisioned a synthetic strategy as outlined in Scheme 1.

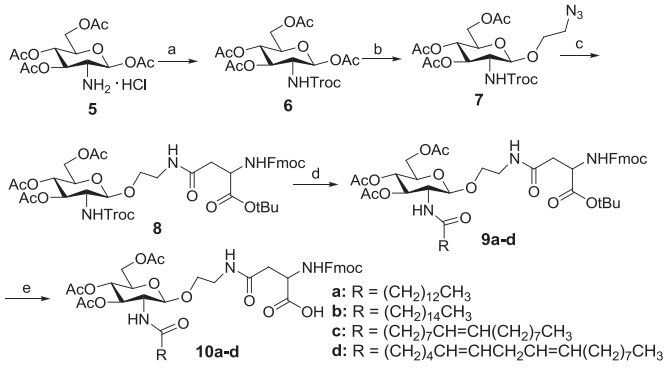
2.2. Synthetic design

Synthetic targets **10a**–**d** have monosaccharide with a long aliphatic chain attached to their asparagine side chain. They were key intermediates for the synthesis of target compounds, and our first undertaking was to prepare **10a**–**d** (Scheme 2). The synthesis of



Scheme 1. Synthesis of full protected lipo-glyco asparagine derivatives.

10a–**d**, as shown in Scheme 2, started from 2-amino-2-deoxy-D-glucose hydrochloride **5**. Firstly, **5** was transformed into compound **6** by well established procedures.[14] Then, the free amino group was protected with a 2,2,2-trichloroethoxycarbonyl (Troc) group, which could be easily removed by zinc.[15] The azide ethyl side chain was introduced into the glucosamine using $BF_3 \cdot Et_2O$ as a catalyst to afford the compound **7**. Next, the azido group was selectively reduced in the condition of Pd/C (10%)/CH_3OH, followed by coupling with Fmoc-Asp-OtBu to afford the compound glycosylated amino acid **8**. Further, when the Troc protected group was cleavaged in the condition of Zn/CH_3COOH, the free amino group can be coupled with fatty acids to afford the key intermediate **9a**–**d**. Finally, the ^{t}Bu group was removed with TFA and the key intermediate **9a**–**d** were converted into the full acetyl protected lipoglycosylated amino acids **10a**–**d**.



Scheme 2. The synthesis of full protected lipo-glyco amino acids. *Reagents and conditions*: (a) 1,1,1-trichloro-2-(chloromethoxy) ethane, $NaHCO_3$, DCM, 70%; (b) 2-azidoethanol, BF_3Et_2O, DCM, 68%; (c) Pd/C (10%), CH_3OH, 78%; then Fmoc-Asp-OtBu, DIC, HOBt, DCM, DMF, 48%; (d) Zn, CH_3COOH; then lipo-acid, DIC, HOBt, DCM, DMF; (e) TFA: DCM=1:3.

2.3. Synthesis of the title compounds

From a retrosynthetic point of view, any peptide bond of the cyclic peptide can be cleaved to offer a linear structure to work with, so theoretically SPPS can start from any amino acid in the ring. Practically, however, various synthetic plans can give different results.[16] In the case of lipoglycopeptides synthesis, it is readily imaginable that the lipoglycosylated amino acids should be installed at a later stage so as to reduce any potential interferences caused by the lipo-glycans and to facilitate manual installation of the lipoglycosylated amino acids, if necessary.

In our synthesis of the title compounds, we chose to construct the linear peptide/glycopeptides with 2-chlorotrityl resin as the solid-phase support and Phe as the first amino acid to install.[17] In