Chemical & Physical Sciences
UNIVERSITY OF TORONTO
MISSISSAUGA

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IB250

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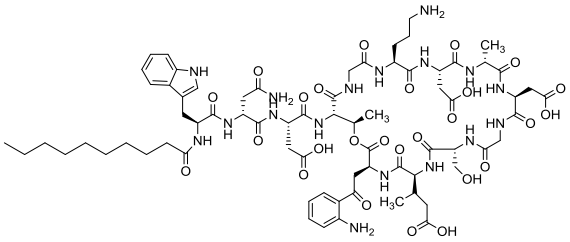
Daptomycin: Total Synthesis and Mechanism of Action Studies using Fluorescent Analogs



Daptomycin

Daptomycin (Dap), a natural product isolated from fermentations of *Streptomyces roseosporus*, is the first and only approved member of a novel class of Ca^{+2}-dependent antibiotics known as cyclic lipodepsipeptides. Dap was approved in in 2003 for the treatment of complicated skin and skin structure infections caused by Gram-positive bacteria. It is not effective against community-acquired pneumonia due to inhibition by pulmonary surfactant. Over the last several years, Dap-resistant bacteria have emerged. This has caused considerable alarm in the medical community as Dap is often used as a last defence against serious infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecium* (VRE). Although Dap was first discovered in the early 1980's, fundamental aspects of its mechanism of action (MOA) remain unknown. Some studies suggest that Dap forms oligomeric pores in bacterial membranes, which results in dissipation of membrane potential and cell death. However, this MOA has yet to be firmly established. The development of a solid-phase approach to the synthesis of Dap and it analogs would greatly facilitate SAR studies, which would in turn expedite MOA investigations and the search for cyclic lipodepsipeptide antibiotics with improved activity and decreased bacterial resistance. Here we present a solid-phase approach to the total synthesis of Dap. This methodology was applied to the synthesis of Dap analogs including Dap analogs bearing fluorescent labels. Membrane binding studies with the fluorescent Dap analogs provided crucial insights into Dap's MOA.