
Divergent Solid-Phase Synthesis of Natural Product-Inspired Bipartite Cyclodepsipeptides: Total Synthesis of Seragamide A


SPS of Seragamide A via Relay-Ring-Closing Metathesis

**Significance:** The authors present the first total synthesis of seragamide A (isolated from the sponge *Suberites japonicus* Thiele in 2006) via a solid-phase synthesis–cyclorelease strategy utilizing relay-ring-closing metathesis. Starting from resin *(E/Z)*-1, the precursor *(E/Z)*-2 was prepared in seven steps. Relay-ring-closing metathesis of *(E/Z)*-2 proceeded in the presence of RuCl₂(SiMes)₃(PCy₃)(=CHPh) (3) to give *(E/Z)*-6 in 34% yield based on *(E/Z)*-1 as a mixture of separable isomers. Treatment of *(E)*-6 with TFA followed by TBAF provided *(E)*-7 (seragamide A) in 65% yield (based on the crucial ring-closing step). Similarly, *(Z)*-6 was converted into *(Z)*-7 in 59% yield.

**Comment:** The present synthetic protocol was also applied to the preparation of a collection of structurally diverse cyclodepsipeptides using various peptides (9 examples) and ketide segments (4 examples).