Herein, an effective protocol for solid-phase synthesis of peptidethiolactones by concomitant ring closure and cleavage from the solid support is reported. The strategy was applied for mapping the importance of the structural features in S. schleiferi AIP (5) by performing an alanine scan and truncation of this natural compound. This furnished some of the most potent inhibitors of accessory gene regulator (agr)-I in the human pathogen S. aureus reported to date.

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