Efforts Toward the Total Synthesis of (-)-Crambidine

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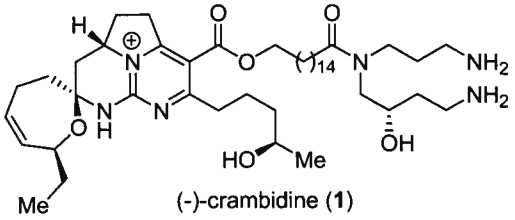
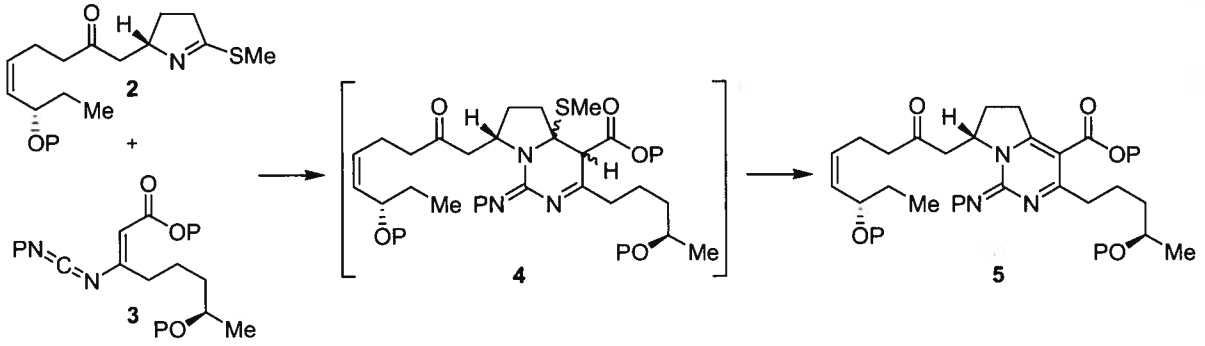
The crambescidin alkaloids, isolated from the Caribbean marine sponge *Crambe crambe*, constitute a structurally distinct family of guanidine alkaloids that has shown a wide range of biological activity. Members of this family have displayed antiviral (HIV, *Herpes simplex*) and antifungal activity (*Candida albicans*). Additionally, the crambescidins are cytotoxic to a variety of cancer cell types (murine leukemia, lung carcinoma, colon carcinoma, and melanoma) at nanomolar concentrations.



(-)-crambidine (**1**)

(-)-Crambidine (**1**) is a unique member of the crambescidin alkaloids that has not been evaluated for biological activity. A synthetic approach to **1** would provide access to the natural product and facilitate a thorough assessment of its biological activity. It was envisioned that a [4+2] annulation strategy, utilizing thioimidate **2** and vinyl carbodiimide **3**, could provide for a highly convergent approach to the core of **1**.



This key [4+2] annulation reaction most likely proceeds via the transient bicyclic intermediate **4**, which would eliminate methanethiol to provide bicyclic guanidine **5**. This approach has been successfully applied to the preparation of **5**, and efforts are currently underway to convert this advanced intermediate into (-)-crambidine (**1**).