

## Enantioselective Total Synthesis of the Kibdelones

John R. Butler, Ph.D.

The University of Texas Southwestern Medical Center at Dallas, 2011

Graduate School of Biomedical Sciences

Supervising Professor: Joseph M. Ready, Ph.D.

Date Available: 1/14/2014

Biological Chemistry

<http://hdl.handle.net/2152.5/1016>

Bibliography: pp. 31-35, 125-130

Keywords: Kibdelones, natural product synthesis, C-H arylation, aromatic polyketides, NCI 60, total synthesis

The kibdelones are a family of aromatic polyketides reported in 2006 by Capon and co-workers. These compounds possess potent antibiotic and cytotoxic activities and operate via an unknown and potentially unique mode of action. In order to fully investigate these properties the kibdelones were targeted for total synthesis. Novel methods for heterocycle synthesis and biaryl bond formation were also targeted as part of the synthesis. The kibdelones contain a chlorinated isoquinolinone and stereogenically rich tetrahydroxanthone heterocycles, which make them challenging synthetic targets. To synthesize these compounds a convergent strategy has been developed that splits the molecule into two fragments of similar size. The isoquinolinone moiety was synthesized from amino acid and benzoic acid fragments using a Pomeranz-Fritsch reaction. Our approach to synthesize the tetrahydroxanthone fragment took advantage of an element of latent C<sub>2</sub> symmetry present in the kibdelones. Using the Shi-epoxidation this fragment was synthesized in an enantioselective fashion from resorcinol. After joining these fragments with sequential Sonogashira reactions a demanding late stage C-H arylation reaction was used to forge the final C-C bond of the natural product. Importantly, this biaryl bond formation was enabled by the serendipitous discovery of a selective copper-catalyzed iodination reaction. All of these efforts led to the successful 20-step synthesis of (-)-kibdelone C, setting the stage for further biological enquiry of these exciting natural products.



<https://repositories.tdl.org/utswmed-ir/admin/item?itemID=2640>