DEVELOPMENT OF A TOTAL SYNTHESIS OF CEBULACTAMS A1 AND A2

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The cebulactams A1 and A2 were isolated from an extract of the marine species *Saccharopolyspora cebuensis* in 2008 by Pimentel-Elardo *et al.* These polyketides consist of a 13-membered macrolactam, a highly-substituted chromane moiety, five stereocenters and a double bond, which is (E)-configured in cebulactam A1 and (Z)-configured in cebulactam A2, as shown in figure 1 [1].

As part of a major project on macrolactam antibiotics, we envisaged a total synthesis program based on a retrosynthesis that commences with a copper-catalyzed Goldberg-type cyclization of an aryl iodide and a primary amide. The eastern part of the molecule is prior coupled to the chromane moiety by a Julia-Kocienski olefination, enabling the synthesis of both stereoisomers of cebulactam. The chromane core itself is synthesized by a Diels-Alder reaction under high pressure conditions, followed by a retro-Diels-Alder reaction and subsequent oxidative aromatization. This novel three-step method is generally useful for the construction of highly-substituted chromanes from pyrans [2].

![Figure 1: a) Structure of the cebulactams. b) Retrosynthetic approach towards cebulactams.](image)

Here we present our progress in the forward synthesis of cebulactam with focus on the recent advances of the Diels-Alder and olefination reactions.

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