Towards the Total Synthesis of the Leishmanicidal Lindbergin E for the Development of a Novel Phloroglucinol-Derived Asymmetric Cyclic Polyketide Synthesis

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The recent characterization of the natural product Lindbergin E (a novel prenylated acylphloroglucinol heterodimer with leishmanicidal activity) by Socolsky et al. presents a promising alternative to traditional treatment of the painful tropical disease Leishmaniasis. Current treatment options have very high failure rates, so the development of a new treatment is crucial. The unique phloroglucinol-derived asymmetric polyketide moiety (PDAP) within Lindbergin E also opens the door to the development of a novel preparation of the previously unexplored moiety by utilizing a formyl group as both a blocking group to prevent poly-prenylation in the electrophilic aromatic substitution-type prenylation and as a fragment-coupling moiety. The development of a novel PDAP synthesis would allow the total-synthesis of over 16 different classes of unexplored natural products. A convergent-synthesis was used due to the sensitivity of the methylene bridge in the final Lindbergin E along with the resulting improved yields. Both fragments (A and B) will be joined using a three-component reductive alkylation coupling followed by demethylation of the methoxy groups with boron tribromide. Fragment A consisted of the 2H-benzopyran core, synthesized with high yield (95%) on the gram scale using a unique co-catalyst system, and a butanoyl substituent added using a Friedel-Crafts acylation. Fragment B was prepared from phloroglucinol, which was converted to 2-methylphloroglucinol using a Vilsmeier-Haack reaction and a successive Clemmensen reduction. The resulting product will be acylated and successively formylated. This will then be prenylated in a novel monoselective PDAP-synthesis, which will be studied extensively in kinetic and thermodynamic studies for reaction optimization.