

# Phase II: Towards the Total Synthesis of the Leishmanicidal Lindbergin E for the Development of an Enantioselective Phloroglucinol-Derived Polyketide Synthesis

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The recent characterization of a new class of prenylated acylphloroglucinol heterodimers (Lindbergins) with leishmanicidal activity by Socolsky et al. presents a promising alternative to traditional treatments for leishmaniasis, such as pentavalent antimony (up to 39% failure rates). Herein, I report the schematics and work towards the total synthesis of Lindbergin E. An A/B convergent synthesis was used due to the sensitivity of the methylene bridge in Lindbergin E along with added simplicity and higher yields. Fragment A, prepared in Phase I, consists of the 2H-benzopyran core, synthesized with high yield (95%) on the gram scale using a boronic acid-mediated cyclization followed by a Friedel-Crafts acylation. Fragment B, the focus of Phase II, was prepared from phloroglucinol, which was methylated using a Vilsmeier-Haack formylation and successive Clemmensen reduction (23% overall). The resulting product was acylated (54%) and successively formylated in acceptable yield (37%) and high purity (>99%). The alkylation of Fragment B will result in the phloroglucinol-derived asymmetric polyketide moiety (PDAP), a valuable structural feature not yet synthesized asymmetrically. I hypothesized that the PDAP moiety could be prepared enantioselectively by modifying the traditional racemic  $S_NAr$  alkylation by utilizing either a modified asymmetric organometallic benzene complex, a chiral diester auxiliary, or a chiral boronic ester auxiliary. These routes are currently being explored. The combination of fragment A and the PDAP moiety (from fragment B) will proceed via a three-component reductive alkylation via the previously installed formyl groups. Lindbergin E will be obtained after the removal of the phenolic methyl groups using boron tribromide.

## Awards Won:

Third Award of \$1,000

American Chemical Society: First Award of \$4,000