Towards the Total Synthesis of the TRAIL-Resistance-Overcoming Pannokin D for the Development of a Pharmaceutically Significant Diprenylated Chromone-Derived Flavonoid Synthesis

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The recent discovery of the natural product Pannokin D (a benzoxanthone-type diprenylated flavonoid with cytotoxic properties and the rare biochemical capability of overcoming tumor necrosis factor-related apoptosis-inducing ligand resistance) by Toume et al. presents a promising treatment option for gastric cancer. Current treatments contribute to the eight hundred thousand deaths caused by gastric cancer yearly as they involve chemotherapeutics with high failure rates and harmful radiotherapy treatments. In this study, the first proposed schematics for the total synthesis of Pannokin D are reported. The synthesis of Pannokin D presents a novel method for preparing the unique diprenylated chromone moiety it possesses which sets the stage for the development of over twenty-five different classes of highly unexplored pharmaceutically relevant natural products. In this year's study, a Friedel-Crafts acylation, rather than a 2H-chromene synthesis, catalyzed by aluminum trichloride and reacting phloroglucinol with acetyl chloride for the synthesis of acetylphloroglucinol has been optimized as the first step towards the total synthesis of Pannokin D. Upon the successful synthesis of acetylphloroglucinol, a Vilsmeier-Haack formylation reacting acetylphloroglucinol with boron trifluoride diethyl etherate and methanesulfonyl chloride will be completed to afford 5,7-dihydroxychromen-4-one. It is hypothesized that subsequent cyclization with 5,7-dihydroxychromen-4-one will afford 7-(1',1'-dimethylpropargyloxy)-5-hydroxychromone. 7-(1',1'-dimethylpropargyloxy)-5-hydroxychromone will then be reacted in DMF to produce a chromone derivative observed in Pannokin D. This chromone derivative will be successively prenylated and reacted for addition of the phloroglucinol derivative.

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