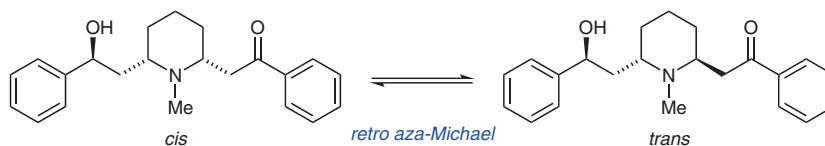
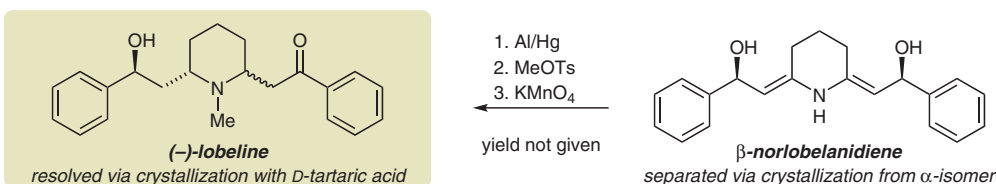
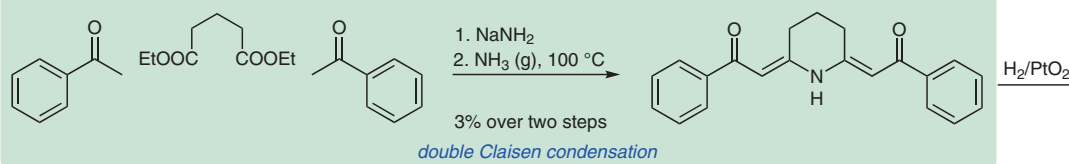


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Synthesis of the Lobelia Alkaloids (*Synthesen der Lobelia-Alkaloide*)*Justus Liebig's Ann. Chem.* **1929**, 473, 102–118, DOI: 10.1002/jlac.19294730106.

Synthesis Confirming Structure: The Lobelia Alkaloids

Key reaction:



Significance: Natural product synthesis can facilitate structural assignment, expand access to rare molecules, and enable synthetic diversification useful for medicinal studies. Structural assignment was particularly important in the early days of chemistry when fewer characterization techniques were available. Knowing from traditional medicine that *Lobelia* alkaloids derived from plants such as Devil's tobacco elicit hallucinogenic and narcotic effects, the group of Heinrich Wieland sought to determine the structure of the bioactive component(s). This marks the first synthesis of this captivating target that henceforth has been the subject of numerous alternative routes, including an industrial multi-kilogram scale synthesis by Boehringer Ingelheim.

Comment: Preceding this study, Wieland and co-workers extensively investigated naturally isolated lobeline and proposed corrections to its previously assigned structure. Confident in their reassignment, they pursued the total synthesis of lobeline to confirm their newly proposed structure. Leveraging the inherent symmetry of lobeline, their direct synthesis begins with a double Claisen condensation between diethyl glutarate and two equivalents acetophenone, establishing the entire carbon skeleton. Subsequent installation of ammonia completes the piperidine core. Finally, redox manipulations and methylation afford precursors norlobelanidiene, norlobelanidine, and lobelanidine, as well as product lobeline upon mono-oxidation with KMnO₄. Crystallization with D-tartaric acid resolves pure (-)-lobeline. Their sample contained both *cis* and *trans* epimers formed via retro aza-Michael chemistry.