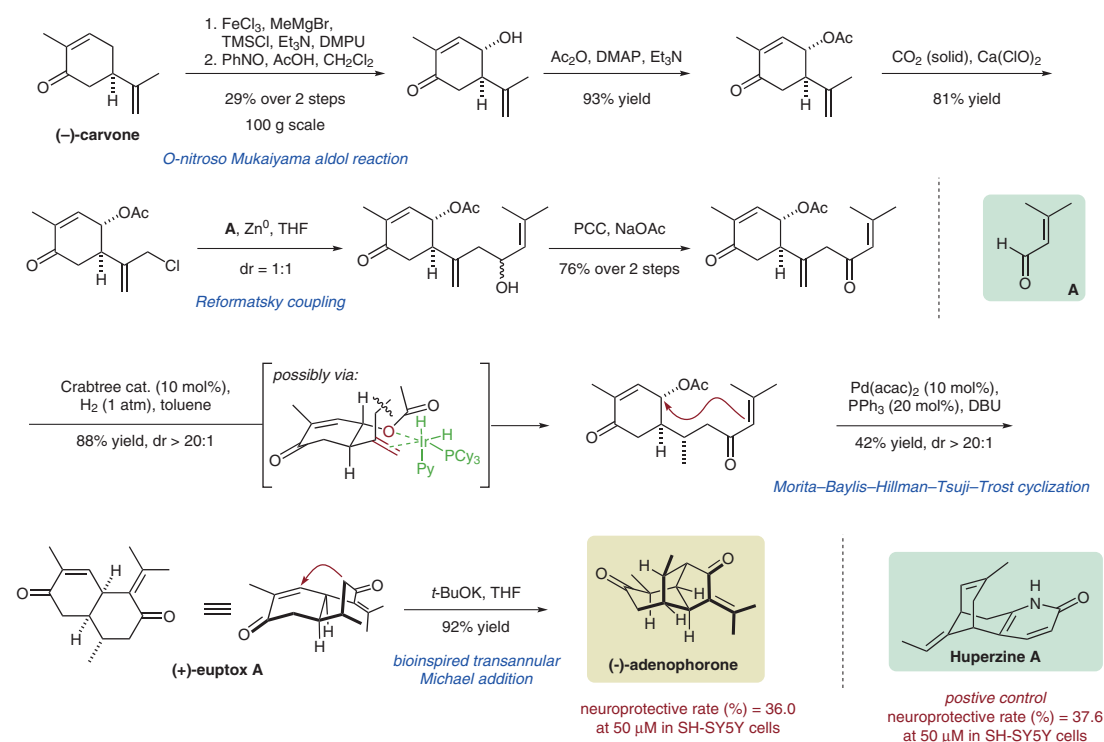


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Adenophorone, An Unprecedented Sesquiterpene from *Eupatorium adenophorum*: Structural Elucidation, Bioinspired Total Synthesis and Neuroprotective Activity Evaluation

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Bioinspired Total Synthesis and Bioactivity Evaluation of a Novel Sesquiterpene (–)-Adenophorone



Significance: Neurodegenerative diseases (NDs), such as Alzheimer's disease and Parkinson's disease, have gained public attention. Excessive formation of reactive oxygen species can result in oxidative stress, a common cause of NDs. In light of studies finding new natural neuroprotective agents, the authors isolated (–)-adenophorone, a sesquiterpene with an unprecedented tricyclo[4.3.1.0^{5,9}]decane skeleton, from *Eupatorium adenophorum*. The structure of (–)-adenophorone is established with X-ray and spectroscopic analysis. A concise total synthesis is accomplished in nine steps, starting with commercially available (–)-carvone.

Comment: The nine-step synthesis features a sequential Reformatsky/oxidation/regio- and stereo-selective hydrogenation with Crabtree's catalyst. The subsequent MBH–Tsuji–Trost cyclization yields (+)-euptox A, which undergoes a Robinson annulation to give (–)-adenophorone with a high yield. The bioinspired Michael addition further validates the hypothesis that (–)-adenophorone could be biosynthetically generated from cadinene sesquiterpene (+)-euptox A. (–)-Adenophorone also shows potent neuroprotective activity in H₂O₂-treated SH-SY5Y and PC12 cells. The efficient synthetic strategy is expected to provide access to other structurally similar sesquiterpenes in the future.

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