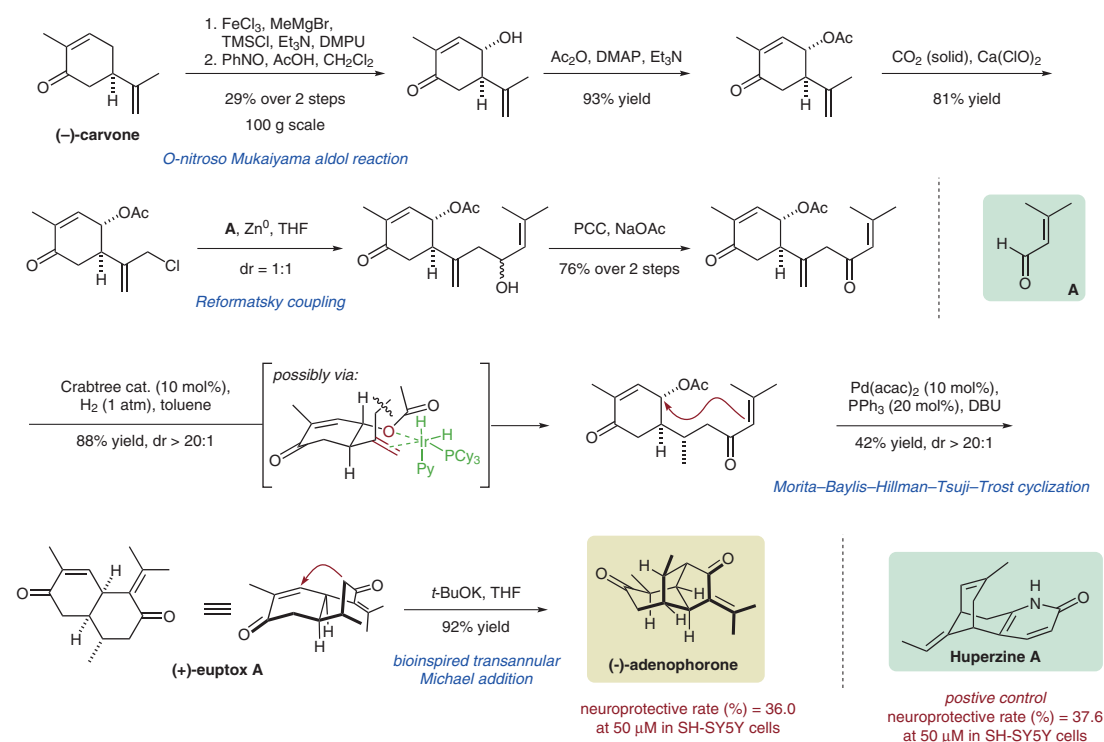B. YIN, X. LI, Z.-X. LI, X.-X. ZHU, L. ZHANG, X.-L. ZHOU, J.-B. XU, F.-Z. CHEN, P. TANG*, F. GAO* (SICHUAN UNIVERSITY AND SOUTHWEST JIAOTONG UNIVERSITY, CHENGDU, P. R. OF CHINA)

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[4.3.1.05,9]decane skeleton, from *Eupatorium adenopharum*. 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 stereoselective 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 H_2O_2-treated SH-SY5Y and PC12 cells. The efficient synthetic strategy is expected to provide access to other structurally similar sesquiterpenes in the future.