Total Synthesis of Isomalabaricane Triterpenoids

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Rhabdastrellic acid A and stelletin E are among the flagship members of the isomalabaricane triterpenoids, a rare family of marine natural products that continue to attract attention for their remarkably specific antitumor properties. These selective apoptosis inducers boast nanomolar mean GI_{50} concentrations against the NCI-60 Human Tumor Cell Lines panel, but with a range that spans 3 orders of magnitude. The stelletins have been heralded as promising lead compounds for targeted therapy, with stelletin E exhibiting a 117-fold increase in potency against p21-deficient HCT-116 human colon cancer cell lines when compared with the wildtype. Nonetheless, and despite several impressive efforts, the isomalabaricanes have yet to succumb to total synthesis in the 38 years since their first isolation. This is perhaps due to the complexity of their *trans-syn-trans*-perhydrobenz[*e*]indene core, whose imposing strain and unorthodox boat–boat conformation stymies many of the traditional synthetic techniques for constructing polycyclic terpene systems. This singular motif has never been prepared in a selective fashion through chemical synthesis.

Here we present the first total syntheses of (±)-rhabdastrellic acid A and (±)-stelletin E, highly cytotoxic isomalabaricane triterpenoids, in a linear sequence of 14 steps from commercial geranylacetone. Their exceptionally strained *trans-syn-trans*-perhydrobenz[*e*]indene core is efficiently accessed in a selective manner through a rapid, complexity-generating sequence featuring a reductive radical polyene cyclization, an unprecedented oxidative Rautenstrauch cycloisomerization, and umpolung α-substitution of a *p*-toluenesulfonylhydrazone with *in situ* reductive transposition. A late-stage cross-coupling in concert with a modular approach to polyunsaturated side chains renders this a general strategy for the synthesis of numerous family members of these synthetically challenging and hitherto inaccessible marine triterpenoids.